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FACULTE DE MEDECINE DE STRASBOURG

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THESE
PRESENTEE POUR LE DIPLOME DE
DOCTEUR EN MEDECINE

Diplôme d'État
Mention Oncologie option Oncologie Radiothérapie

PAR

Chloé-Line JEANDIDIER
Née le 13 septembre 1988 à STRASBOURG

EXISTE-T-IL UNE RADIOTHERAPIE FUTILE ?

Caractéristiques cliniques des patients décédés à moins de deux mois d'une irradiation curative ou palliative et réflexion éthique sur le traitement par radiothérapie des malades en fin de vie

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Président et Directeur de Thèse : Georges NOËL, Professeur

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CLAVERT Philippe P0044	NRPô CS	• Pôle de l'Appareil locomoteur - Service d'Orthopédie / CCOM d'Illkirch	42.01	Anatomie (option clinique, orthopédie traumatologique)
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de SEZE Jérôme P0057	NRPô NCS	• Pôle Tête et Cou - CETD - Service de Neurologie / Hôpital de Hautepierre	49.01	Neurologie
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EHLINGER Matfhieu P0188	NRPô NCS	• Pôle de l'Appareil Locomoteur - Service de Chirurgie Orthopédique et de Traumatologie/Hôpital de Hautepierre	50.02	Chirurgie Orthopédique et Traumatologique
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Mme FACCA Sybille P0179	NRPô NCS	• Pôle de l'Appareil locomoteur - Service de la Main et des Nerfs périphériques / CCOM Illkirch	50.02	Chirurgie orthopédique et traumatologique
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Mme HELMS Julie M0114 / P0209	NRPô NCS	• Pôle Urgences - Réanimations médicales / Centre antipoison - Service de Réanimation Médicale / Nouvel Hôpital Civil	48.02	Médecine Intensive-Réanimation
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LANGER Bruno P0091	RPô NCS	• Pôle de Gynécologie-Obstétrique - Service de Gynécologie-Obstétrique / Hôpital de Hautepierre	54.03	**Gynécologie-Obstétrique** ; gynécologie médicale : option gynécologie-Obstétrique
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MALOUF Gabriel P0203	NRPô NCS	• Pôle d'Onco-hématologie - Service d'Hématologie et d'Oncologie / Hôpital de Hautepierre	47.02	**Cancérologie** ; Radiothérapie Option : Cancérologie
MARK Manuel P0098	NRPô NCS	• Pôle de Biologie - Laboratoire de Cytogénétique, Cytologie et Histologie quantitative / Hôpital de Hautepierre	54.05	Biologie et médecine du développement et de la reproduction (option biologique)
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Mme OLLAND Anne P0204	NRPô NCS	• Pôle de Pathologie Thoracique - Service de Chirurgie thoracique / Nouvel Hôpital Civil	51.03	Chirurgie thoracique et cardio-vasculaire
Mme PAILLARD Catherine P0180	NRPô CS	• Pôle médico-chirurgicale de Pédiatrie - Service de Pédiatrie III / Hôpital de Hautepierre	54.01	Pédiatrie
PELACCIA Thierry P0205	NRPô NCS	• Pôle d'Anesthésie / Réanimation chirurgicales / SAMU-SMUR - Service SAMU/SMUR / HP	48.05	Réanimation ; **Médecine d'urgence** Option : Médecine d'urgences
Mme PERRETTA Silvana P0117	NRPô NCS	• Pôle Hépato-digestif de l'Hôpital Civil - Service d'Urgence, de Chirurgie Générale et Endocrinienne / NHC	52.02	Chirurgie digestive
PESSAUX Patrick P0118	NRPô NCS	• Pôle des Pathologies digestives, hépatiques et de la transplantation - Service d'Urgence, de Chirurgie Générale et Endocrinienne / NHC	53.02	Chirurgie Générale
PETIT Thierry P0119	CDp	• Centre Régional de Lutte Contre le Cancer - Paul Strauss (par convention) - Département de médecine oncologique	47.02	**Cancérologie** ; Radiothérapie Option : Cancérologie Clinique
PIVOT Xavier P0206	NRPô NCS	• Centre Régional de Lutte Contre le Cancer - Paul Strauss (par convention) - Département de médecine oncologique	47.02	**Cancérologie** ; Radiothérapie Option : Cancérologie Clinique
POTTECHER Julien P0181	NRPô NCS	• Pôle d'Anesthésie / Réanimations chirurgicales / SAMU-SMUR - Service d'Anesthésie et de Réanimation Chirurgicale / Hôpital de Hautepierre	48.01	**Anesthésiologie-réanimation** ; Médecine d'urgence (option clinique)
PRADIGNAC Alain P0123	NRPô NCS	• Pôle de Médecine Interne, Rhumatologie, Nutrition, Endocrinologie, Diabétologie (MIRNED) - Service de Médecine interne et nutrition / HP	44.04	Nutrition
PROUST François P0182	NRPô CS	• Pôle Tête et Cou - Service de Neurochirurgie / Hôpital de Hautepierre	49.02	Neurochirurgie
Pr RAUL Jean-Sébastien P0125	NRPô CS	• Pôle de Biologie - Service de Médecine Légale, Consultation d'Urgences médico-judiciaires et Laboratoire de Toxicologie / Faculté et NHC • Institut de Médecine Légale / Faculté de Médecine	46.03	Médecine Légale et droit de la santé
REIMUND Jean-Marie P0126	NRPô NCS	• Pôle des Pathologies digestives, hépatiques et de la transplantation - Service d'Hépato-Gastro-Entérologie et d'Assistance Nutritive / HP	52.01	Option : Gastro-entérologie
Pr RICCI Roméo P0127	NRPô NCS	• Pôle de Biologie - Laboratoire de Biochimie et de Biologie moléculaire / HP	44.01	Biochimie et biologie moléculaire
ROHR Serge P0128	NRPô CS	• Pôle des Pathologies digestives, hépatiques et de la transplantation - Service de Chirurgie générale et Digestive / HP	53.02	Chirurgie générale
Mme ROSSIGNOL -BERNARD Sylvie PO196	NRPô CS	• Pôle médico-chirurgical de Pédiatrie - Service de Pédiatrie I / Hôpital de Hautepierre	54.01	Pédiatrie
ROUL Gérald P0129	NRPô NCS	• Pôle d'activité médico-chirurgicale Cardio-vasculaire - Service de Cardiologie / Nouvel Hôpital Civil	51.02	Cardiologie
Mme ROY Catherine P0140	NRPô CS	• Pôle d'Imagerie - Serv. d'Imagerie B - Imagerie viscérale et cardio-vasculaire / NHC	43.02	Radiologie et imagerie médicale (opt clinique)

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SANANES Nicolas P0212	NRPô CS	• Pôle de Gynécologie-Obstétrique - Service de Gynécologie-Obstétriquel/ HP	54.03	**Gynécologie-Obstétrique** ; gynécologie médicale Option : Gynécologie-Obstétrique
SAUDER Philippe P0142	NRPô CS	• Pôle Urgences - Réanimations médicales / Centre antipoison - Service de Réanimation médicale / Nouvel Hôpital Civil	48.02	Réanimation
SAUER Arnaud P0183	NRPô NCS	• Pôle de Spécialités médicales - Ophtalmologie / SMO - Service d'Ophtalmologie / Nouvel Hôpital Civil	55.02	Ophtalmologie
SAULEAU Erik-André P0184	NRPô NCS	• Pôle de Santé publique et Santé au travail - Laboratoire de Biostatistiques / Hôpital Civil • Biostatistiques et Informatique / Faculté de médecine / HC	46.04	Biostatiqtiques, Informatique médicale et Technologies de Communication (option biologique)
SAUSSINE Christian P0143	RPô CS	• Pôle d'Urologie, Morphologie et Dermatologie - Service de Chirurgie Urologique / Nouvel Hôpital Civil	52.04	Urologie
SCHNEIDER Francis P0144	RPô CS	• Pôle Urgences - Réanimations médicales / Centre antipoison - Service de Réanimation médicale / Hôpital de Hautepierre	48.02	Réanimation
Mme SCHRÖDER Carmen P0185	NRPô CS	• Pôle de Psychiatrie et de santé mentale - Service de Psychothérapie pour Enfants et Adolescents / Hôpital Civil	49.04	**Pédopsychiatrie** ; Addictologie
SCHULTZ Philippe P0145	NRPô NCS	• Pôle Tête et Cou - CETD - Serv. d'Oto-rhino-laryngologie et de Chirurgie cervico-faciale / HP	55.01	Oto-rhino-laryngologie
SERFATY Lawrence P0197	NRPô NCS	• Pôle des Pathologies digestives, hépatiques et de la transplantation - Service d'Hépato-Gastro-Entérologie et d'Assistance Nutritive / HP	52.01	Gastro-entérologie ; Hépatologie ; Addictologie Option : **Hépatologie**
SIBILIA Jean P0146	NRPô NCS	• Pôle de Médecine Interne, Rhumatologie, Nutrition, Endocrinologie, Diabétologie (MIRNED) - Service de Rhumatologie / Hôpital Hautepierre	50.01	Rhumatologie
Mme SPEEG-SCHATZ Claude P0147	RPô CS	• Pôle de Spécialités médicales - Ophtalmologie / SMO - Service d'Ophtalmologie / Nouvel Hôpital Civil	55.02	Ophtalmologie
STEIB Jean-Paul P0149	NRPô CS	• Pôle de l'Appareil locomoteur - Service de Chirurgie du rachis / Hôpital Civil	50.02	Chirurgie orthopédique et traumatologique
STEPHAN Dominique P0150	NRPô CS	• Pôle d'activité médico-chirurgicale Cardio-vasculaire - Service des Maladies vasculaires - HTA - Pharmacologie clinique / Nouvel Hôpital Civil	51.04	Option : Médecine vasculaire
THAVEAU Fabien P0152	NRPô NCS	• Pôle d'activité médico-chirurgicale Cardio-vasculaire - Service de Chirurgie vasculaire et de transplantation rénale / NHC	51.04	Option : Chirurgie vasculaire
Mme TRANCHANT Christine P0153	NRPô CS	• Pôle Tête et Cou - CETD - Service de Neurologie / Hôpital de Hautepierre	49.01	Neurologie
VEILLON Francis P0155	NRPô CS	• Pôle d'Imagerie - Service d'Imagerie 1 - Imagerie viscérale, ORL et mammaire / Hôpital Hautepierre	43.02	Radiologie et imagerie médicale (option clinique)
VELTEN Michel P0156	NRPô NCS CS	• Pôle de Santé publique et Santé au travail - Département de Santé Publique / Secteur 3 - Epidémiologie et Economie de la Santé / Hôpital Civil • Laboratoire d'Epidémiologie et de santé publique / HC / Fac de Médecine • Centre de Lutte contre le Cancer Paul Strauss - Serv. Epidémiologie et de biostatistiques	46.01	Epidémiologie, économie de la santé et prévention (option biologique)
VETTER Denis P0157	NRPô NCS	• Pôle de Médecine Interne, Rhumatologie, Nutrition, Endocrinologie, Diabétologie (MIRNED) - Service de Médecine Interne, Diabète et Maladies métaboliques/HC	52.01	Option : Gastro-entérologie
VIDAILHET Pierre P0158	NRPô NCS	• Pôle de Psychiatrie et de santé mentale - Service de Psychiatrie I / Hôpital Civil	49.03	Psychiatrie d'adultes
VIVILLE Stéphane P0159	NRPô NCS	• Pôle de Biologie - Laboratoire de Parasitologie et de Pathologies tropicales / Fac. de Médecine	54.05	Biologie et médecine du développement et de la reproduction (option biologique)
VOGEL Thomas P0160	NRPô CS	• Pôle de Gériatrie - Service de soins de suite et réadaptations gériatriques / Hôpital de la Robertsau	51.01	Option : Gériatrie et biologie du vieillissement
WEBER Jean-Christophe Pierre P0162	NRPô CS	• Pôle de Spécialités médicales - Ophtalmologie / SMO - Service de Médecine Interne / Nouvel Hôpital Civil	53.01	Option : Médecine Interne
WOLF Philippe P0207	NRPô NCS	• Pôle des Pathologies digestives, hépatiques et de la transplantation - Service de Chirurgie Générale et de Transplantations multiorganes / HP - Coordonnateur des activités de prélèvements et transplantations des HU	53.02	Chirurgie générale
Mme WOLFF Valérie P0001	NRPô NCS	• Pôle Tête et Cou - Service de Neurochirurgie / Hôpital de Hautepierre	49.01	Neurologie

HC : Hôpital Civil - HP : Hôpital de Hautepierre - NHC : Nouvel Hôpital Civil
* : CS (Chef de service) ou NCS (Non Chef de service hospitalier) Cspi : Chef de service par intérim CSp : Chef de service provisoire (un an)
CU : Chef d'unité fonctionnelle
Pô : Pôle RPô (Responsable de Pôle) ou NRPô (Non Responsable de Pôle)
Cons. : Consultanat hospitalier (poursuite des fonctions hospitalières sans chefferie de service) Dir : Directeur
(1) En surnombre universitaire jusqu'au 31.08.2018
(3) (7) Consultant hospitalier (pour un an) éventuellement renouvelable --> 31.08.2017
(5) En surnombre universitaire jusqu'au 31.08.2019 (8) Consultant hospitalier (pour une 2ème année) --> 31.08.2017
(6) En surnombre universitaire jusqu'au 31.08.2017 (9) Consultant hospitalier (pour une 3ème année) --> 31.08.2017

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A4 - PROFESSEUR ASSOCIE DES UNIVERSITES

HABERSETZER François	CS	Pôle Hépato-digestif 4190 Service de Gastro-Entérologie - NHC	52.01	Gastro-Entérologie
CALVEL Laurent	NRPô CS	Pôle Spécialités médicales - Ophtalmologie / SMO Service de Soins palliatifs / NHC	55.02	Ophtalmologie
SALVAT Eric		Centre d'Evaluation et de Traitement de la Douleur		

MO128 B1 - MAITRES DE CONFERENCES DES UNIVERSITES - PRATICIENS HOSPITALIERS (MCU-PH)

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AGIN Arnaud M0001		• Pôle d'Imagerie - Service de Biophysique et de Médecine nucléaire/Hôpital de Hautepierre	43.01	Biophysique et Médecine nucléaire
Mme ANTAL Maria Cristina M0003		• Pôle de Biologie - Service de Pathologie / Hautepierre • Faculté de Médecine / Institut d'Histologie	42.02	Histologie, Embryologie et Cytogénétique (option biologique)
Mme ANTONI Delphine M0109		• Centre de lutte contre le cancer Paul Strauss	47.02	Cancérologie ; **Radiothérapie**
~~ARGEMI Xavier~~ ~~M0112~~ (En disponibilité)		~~• Pôle de Spécialités médicales - Ophtalmologie / SMO~~ ~~- Service des Maladies infectieuses et tropicales / Nouvel Hôpital Civil~~	~~45.03~~	~~Maladies infectieuses ; Maladies tropicales~~ ~~Option : **Maladies infectieuses**~~
Mme AYME-DIETRICH Estelle M0117		• Pôle de Parmacologie - Unité de Pharmacologie clinique / Faculté de Médecine	48.03	**Pharmacologie fondamentale** ; pharmacologie clinique ; addictologie Option : pharmacologie fondamentale
Mme BARNIG Cindy M0110		• Pôle de Pathologie thoracique - Service de Physiologie et d'Explorations Fonctionnelles / NHC	44.02	**Physiologie**
Mme BIANCALANA Valérie M0008		• Pôle de Biologie - Laboratoire de Diagnostic Génétique / Nouvel Hôpital Civil	47.04	Génétique (option biologique)
BLONDET Cyrille M0091		• Pôle d'Imagerie - Service de Biophysique et de Médecine nucléaire/Hôpital de Hautepierre	43.01	Biophysique et médecine nucléaire
BONNEMAINS Laurent M0099		• Pôle d'activité médico-chirurgicale Cardio-vasculaire - Service de Chirurgie cardio-vasculaire / Nouvel Hôpital Civil	54.01	Pédiatrie
BOUSIGES Olivier M0092		• Pôle de Biologie - Laboratoire de Biochimie et de Biologie moléculaire / HP	44.01	Biochimie et biologie moléculaire
CARAPITO Raphaël M0113		• Pôle de Biologie - Laboratoire d'Immunologie biologique / Nouvel Hôpital Civil	47.03	Immunologie
CAZZATO Roberto M0118		• Pôle d'Imagerie - Service d'Imagerie A interventionnelle / NHC	43.02	Radiologie et imagerie médicale (option clinique)
Mme CEBULA Hélène M0124		• Pôle Tête-Cou - Service de Neurochirurgie / HP	49.02	Neurochirurgie
CERALINE Jocelyn M0012		• Pôle d'Oncologie et d'Hématologie - Service d'Oncologie et d'Hématologie / HP	47.02	**Cancérologie** ; Radiothérapie (option biologique)
CHOQUET Philippe M0014		• Pôle d'Imagerie - Service de Biophysique et de Médecine nucléaire / HP	43.01	Biophysique et médecine nucléaire
COLLONGUES Nicolas M0016		• Pôle Tête et Cou-CETD - Centre d'Investigation Clinique / NHC et HP	49.01	Neurologie
DALI-YOUCEF Ahmed Nassim M0017		• Pôle de Biologie - Laboratoire de Biochimie et Biologie moléculaire / NHC	44.01	Biochimie et biologie moléculaire
Mme de MARTINO Sylvie M0018		• Pôle de Biologie - Laboratoire de Bactériologie / PTM HUS et Faculté de Médecine	45.01	**Bactériologie**-virologie Option bactériologie-virologie biologique
~~Mme DEPIENNE Christel~~ ~~M0100~~ (En disponibilité)	CS	~~• Pôle de Biologie~~ ~~- Laboratoire de Cytogénétique / HP~~	~~47.04~~	~~Génétique~~
DEVYS Didier M0019		• Pôle de Biologie - Laboratoire de Diagnostic génétique / Nouvel Hôpital Civil	47.04	Génétique (option biologique)
DOLLÉ Pascal M0021		• Pôle de Biologie -Laboratoire de Biochimie et biologie moléculaire / NHC	44.01	Biochimie et biologie moléculaire
Mme ENACHE Irina M0024		• Pôle de Pathologie thoracique - Service de Physiologie et d'Explorations fonctionnelles / NHC	44.02	Physiologie
FILISETTI Denis M0025		• Pôle de Biologie - Labo. de Parasitologie et de Mycologie médicale / PTM HUS et Faculté	45.02	Parasitologie et mycologie (option biologique)
FOUCHER Jack M0027		• Institut de Physiologie / Faculté de Médecine • Pôle de Psychiatrie et de santé mentale - Service de Psychiatrie I / Hôpital Civil	44.02	Physiologie (option clinique)
GUERIN Eric M0032		• Pôle de Biologie - Laboratoire de Biochimie et de Biologie moléculaire / HP	44.03	Biologie cellulaire (option biologique)
GUFFROY Aurélien M0125		• Pôle de Spécialités médicales - Ophtalmologie / SMO - Service de Médecine interne et d'Immunologie clinique / NHC	47.03	Immunologie (option clinique)
Mme HARSAN-RASTEI Laura M0119		• Pôle d'Imagerie - Service de Biophysique et de Médecine nucléaire / Hôpital de Hautepierre	43.01	Biophysique et médecine nucléaire
Mme HEIMBURGER Céline M0120		• Pôle d'Imagerie - Service de Biophysique et de Médecine nucléaire/Hôpital de Hautepierre	43.01	Biophysique et médecine nucléaire
HUBELE Fabrice M0033		• Pôle d'Imagerie - Service de Biophysique et de Médecine nucléaire / HP et NHC	43.01	Biophysique et médecine nucléaire
Mme JACAMON-FARRUGIA Audrey M0034		• Pôle de Biologie - Service de Médecine Légale, Consultation d'Urgences médico-judiciaires et Laboratoire de Toxicologie / Faculté et HC • Institut de Médecine Légale / Faculté de Médecine	46.03	Médecine Légale et droit de la santé
JEGU Jérémie M0101		• Pôle de Santé publique et Santé au travail - Service de Santé Publique / Hôpital Civil	46.01	Epidémiologie, Economie de la santé et Prévention (option biologique)

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JEHL François M0035		• Pôle de Biologie - Institut (Laboratoire) de Bactériologie / PTM HUS et Faculté	45.01	Option : **Bactériologie**-virologie (biologique)
KASTNER Philippe M0089		• Pôle de Biologie - Laboratoire de diagnostic génétique / Nouvel Hôpital Civil	47.04	Génétique (option biologique)
Mme KEMMEL Véronique M0036		• Pôle de Biologie - Laboratoire de Biochimie et de Biologie moléculaire / HP	44.01	Biochimie et biologie moléculaire
KOCH Guillaume M0126		- Institut d'Anatomie Normale / Faculté de Médecine	42.01	Anatomie (Option clinique)
Mme LAMOUR Valérie M0040		• Pôle de Biologie - Laboratoire de Biochimie et de Biologie moléculaire / HP	44.01	Biochimie et biologie moléculaire
Mme LANNES Béatrice M0041		• Institut d'Histologie / Faculté de Médecine • Pôle de Biologie - Service de Pathologie / Hôpital de Hautepierre	42.02	Histologie, Embryologie et Cytogénétique (option biologique)
LAVAUX Thomas M0042		• Pôle de Biologie - Laboratoire de Biochimie et de Biologie moléculaire / HP	44.03	Biologie cellulaire
LAVIGNE Thierry M0043	CS	• Pôle de Santé Publique et Santé au travail - Service d'Hygiène hospitalière et de médecine préventive / PTM et HUS - Equipe opérationnelle d'Hygiène	46.01	Epidémiologie, économie de la santé et prévention (option biologique)
Mme LEJAY Anne M0102		• Pôle de Pathologie thoracique - Service de Physiologie et d'Explorations fonctionnelles / NHC	44.02	Physiologie (Biologique)
LENORMAND Cédric M0103		• Pôle de Chirurgie maxillo-faciale, Morphologie et Dermatologie - Service de Dermatologie / Hôpital Civil	50.03	Dermato-Vénéréologie
Mme LETSCHER-BRU Valérie M0045		• Pôle de Biologie - Laboratoire de Parasitologie et de Mycologie médicale / PTM HUS • Institut de Parasitologie / Faculté de Médecine	45.02	Parasitologie et mycologie (option biologique)
LHERMITTE Benoît M0115		• Pôle de Biologie - Service de Pathologie / Hôpital de Hautepierre	42.03	Anatomie et cytologie pathologiques
Mme LONSDORFER-WOLF Evelyne M0090		• Institut de Physiologie Appliquée - Faculté de Médecine • Pôle de Pathologie thoracique - Service de Physiologie et d'Explorations fonctionnelles / NHC	44.02	Physiologie
LUTZ Jean-Christophe M0046		• Pôle de Chirurgie plastique reconstructrice et esthétique, Chirurgie maxillo-faciale, Morphologie et Dermatologie - Serv. de Chirurgie Maxillo-faciale, plastique reconstructrice et esthétique/HC	55.03	Chirurgie maxillo-faciale et stomatologie
MEYER Alain M0093		• Institut de Physiologie / Faculté de Médecine • Pôle de Pathologie thoracique - Service de Physiologie et d'Explorations fonctionnelles / NHC	44.02	Physiologie (option biologique)
MIGUET Laurent M0047		• Pôle de Biologie - Laboratoire d'Hématologie biologique / Hôpital de Hautepierre et NHC	44.03	Biologie cellulaire (type mixte : biologique)
Mme MOUTOU Céline ép. GUNTHNER M0049	CS	• Pôle de Biologie - Laboratoire de Diagnostic préimplantatoire / CMCO Schiltigheim	54.05	Biologie et médecine du développement et de la reproduction (option biologique)
MULLER Jean M0050		• Pôle de Biologie - Laboratoire de Diagnostic génétique / Nouvel Hôpital Civil	47.04	Génétique (option biologique)
Mme NICOLAE Alina M0127		• Pôle de Biologie - Service de Pathologie / Hôpital de Hautepierre	42.03	Anatomie et Cytologie Pathologiques (Option Clinique)
NOLL Eric M0111		• Pôle d'Anesthésie Réanimation Chirurgicale SAMU-SMUR - Service Anesthésiologie et de Réanimation Chirurgicale - Hôpital Hautepierre	48.01	**Anesthésiologie-Réanimation** ; Médecine d'urgence
Mme NOURRY Nathalie M0011		• Pôle de Santé publique et Santé au travail - Service de Pathologie professionnelle et de Médecine du travail - HC	46.02	Médecine et Santé au Travail (option clinique)
PENCREAC'H Erwan M0052		• Pôle de Biologie - Laboratoire de Biochimie et biologie moléculaire / Nouvel Hôpital Civil	44.01	Biochimie et biologie moléculaire
PFAFF Alexander M0053		• Pôle de Biologie - Laboratoire de Parasitologie et de Mycologie médicale / PTM HUS	45.02	Parasitologie et mycologie
Mme PITON Amélie M0094		• Pôle de Biologie - Laboratoire de Diagnostic génétique / NHC	47.04	Génétique (option biologique)
PREVOST Gilles M0057		• Pôle de Biologie - Institut (Laboratoire) de Bactériologie / PTM HUS et Faculté	45.01	Option : **Bactériologie**-virologie (biologique)
Mme RADOSAVLJEVIC Mirjana M0058		• Pôle de Biologie - Laboratoire d'Immunologie biologique / Nouvel Hôpital Civil	47.03	Immunologie (option biologique)
Mme REIX Nathalie M0095		• Pôle de Biologie - Labo. d'Explorations fonctionnelles par les isotopes / NHC • Institut de Physique biologique / Faculté de Médecine	43.01	Biophysique et médecine nucléaire
RIEGEL Philippe M0059		• Pôle de Biologie - Institut (Laboratoire) de Bactériologie / PTM HUS et Faculté	45.01	Option : **Bactériologie**-virologie (biologique)
ROGUE Patrick (cf. A2) M0060		• Pôle de Biologie - Laboratoire de Biochimie et biologie moléculaire / NHC	44.01	Biochimie et biologie moléculaire (option biologique)
Mme ROLLAND Delphine M0121		• Pôle de Biologie - Laboratoire d'Hématologie biologique / Hautepierre	47.01	**Hématologie** ; transfusion (type mixte : Hématologie)
ROMAIN Benoît M0061		• Pôle des Pathologies digestives, hépatiques et de la transplantation - Service de Chirurgie générale et Digestive / HP	53.02	Chirurgie générale

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Mme RUPPERT Elisabeth M0106		• Pôle Tête et Cou - Service de Neurologie - Unité de Pathologie du Sommeil / Hôpital Civil	49.01	Neurologie
Mme SABOU Alina M0096		• Pôle de Biologie - Laboratoire de Parasitologie et de Mycologie médicale / PTM HUS • Institut de Parasitologie / Faculté de Médecine	45.02	Parasitologie et mycologie (option biologique)
Mme SCHEIDECKER Sophie M0122		• Pôle de Biologie - Laboratoire de Diagnostic génétique / Nouvel Hôpital Civil	47.04	Génétique
Mme SCHNEIDER Anne M0107		• Pôle médico-chirurgical de Pédiatrie - Service de Chirurgie pédiatrique / Hôpital de Hautepierre	54.02	Chirurgie Infantile
SCHRAMM Frédéric M0068		• Pôle de Biologie - Institut (Laboratoire) de Bactériologie / PTM HUS et Faculté	45.01	Option : **Bactériologie**-virologie (biologique)
Mme SOLIS Morgane M0123		• Pôle de Biologie - Laboratoire de Virologie / Hôpital de Hautepierre	45.01	**Bactériologie-Virologie** ; hygiène hospitalière Option : Bactériologie-Virologie
Mme SORDET Christelle M0069		• Pôle de Médecine Interne, Rhumatologie, Nutrition, Endocrinologie, Diabétologie (MIRNED) - Service de Rhumatologie / Hôpital de Hautepierre	50.01	Rhumatologie
TALHA Samy M0070		• Pôle de Pathologie thoracique - Service de Physiologie et explorations fonctionnelles / NHC	44.02	Physiologie (option clinique)
Mme TALON Isabelle M0039		• Pôle médico-chirurgical de Pédiatrie - Service de Chirurgie Infantile / Hôpital Hautepierre	54.02	Chirurgie infantile
TELETIN Marius M0071		• Pôle de Biologie - Service de Biologie de la Reproduction / CMCO Schiltigheim	54.05	Biologie et médecine du développement et de la reproduction (option biologique)
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En présence des maîtres de cette école,
de mes chers condisciples,
je promets et je jure au nom de l'Être suprême
d'être fidèle aux lois de l'honneur et de la probité
dans l'exercice de la médecine.

Je donnerai mes soins gratuits à l'indigent
et n'exigerai jamais un salaire au- dessus de mon travail.

Admise à l'intérieur des maisons,
mes yeux ne verront pas ce qui s'y passe.

Ma langue taira les secrets qui me seront confiés
et mon état ne servira pas à corrompre les mœurs
ni à favoriser les crimes.

Respectueuse et reconnaissante envers mes maîtres
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis restée fidèle à mes promesses.

Que je sois couverte d'opprobre et méprisée de mes confrères
si j'y manque.

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Supplementary Data

Supplementary Data 1: Patients with Metastatic Disease and treated with Palliative Radiotherapy (n = 929): correlation test results for survival, for variables with significant p value < 0.20 in univariate analysis.

Supplementary Data 2: Patients with Metastatic Disease and treated with Palliative Radiotherapy (n = 929) deceased at 7 days, 30 days and 60 days after radiotherapy: correlation test results for survival, for variables with significant p value < 0.20 in univariate analysis.

ARTICLE 3

Tables

Table 1: Characteristics of patients' population, stratified by Metastatic Status and Therapeutic Objective (Curative or Palliative Radiotherapy)

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Figure 2: Shared Decision Making compared with paternalistic and informative models model with four steps (from Charles et al., 1997)

INTRODUCTION DU TRAVAIL DE THESE

Le concept de "radiothérapie futile" n'est pas d'un usage courant. On ne le retrouve pas dans la littérature médicale, qu'elle soit nationale ou internationale. Il désigne pourtant un problème fréquent dans les services de radiothérapie : la prescription d'un traitement qui n'apportera aucun bénéfice au patient, voire qui ne peut que lui nuire.

Dans ce travail, on se propose d'utiliser le mot "futile" au sens plus anglo-saxon du terme, c'est-à-dire non pas comme un synonyme de "sans valeur, source de gaspillage" mais au sens de "n'avoir aucun effet, être vain". Les anglophones qualifient ainsi de "*futile medical care*" ce que la législation française appelle "obstination déraisonnable", à savoir des actes "inutiles et/ou disproportionnés, et/ou [qui] n'ont d'autre effet que le seul maintien artificiel de la vie"[1]. Cette définition est d'ailleurs placée en opposition à celle des soins palliatifs, qui sont caractérisés comme des " soins actifs et continus […] [qui] visent à soulager la douleur, à apaiser la souffrance psychique, à sauvegarder la dignité de la personne malade et à soutenir son entourage"[2]. Pour les textes de loi, éviter l'obstination déraisonnable sous-entend de promouvoir les soins palliatifs.

Cependant, aussi paradoxal que cela paraisse, ce sont parfois les soins palliatifs eux-mêmes qui exposent au risque de prise en charge futile. L'arrêt établi des traitements curatifs d'un patient ne le garantit pas pour autant d'un soin déraisonnable : ce n'est pas parce qu'un acte n'a plus pour objet "le maintien artificiel de la vie" qu'il ne peut pas être "inutile et/ou disproportionné".

La radiothérapie représente une discipline de choix pour étudier cette problématique. En effet, il s'agit d'un traitement de routine qui, rien qu'en France, concerne plus de 200000 personnes par an. Parmi ces patients, 20% en moyenne sont traités pour des localisations métastatiques ;

[1] Article L1110-5-1 du Code de la santé publique, loi du 2 février 2016
[2] Article L1110-10 du Code de la santé publique, loi du 2 février 2016

on sait en effet qu'en présence de lésions malignes symptomatiques la radiothérapie représente un traitement efficace et bien toléré, qui peut s'appliquer même à des patients à l'état général très altéré, proches de la fin de vie. Néanmoins, ce traitement n'est pas dépourvu d'inconvénients: transports quotidiens, stations prolongées et parfois douloureuses sur la table de traitement, moyens de contention oppressants, visites médicales répétées et éventuels effets secondaires aigus sont autant d'épreuves potentielles. Brèves et tolérables dans la grande majorité des cas, peuvent néanmoins représenter une charge physique et psychique épuisante pour un malade en fin de vie. Enfin, l'effet clinique d'une radiothérapie est le plus souvent retardé, jusqu'à quatre ou huit semaines après le traitement. Il parait donc peu judicieux de proposer ce traitement aux patients les plus fragiles, qui risque de décéder avant même d'avoir pu bénéficier de l'effet symptomatique attendu.

Mais comment peut-on évaluer ce risque à l'avance, au moment de prescrire la radiothérapie ? Quelles sont les caractéristiques cliniques de ces malades ? De quelles ressources objectives le médecin dispose-t-il dans cette réflexion ? Et comment y intégrer le patient, en tenant compte de sa volonté comme de sa vulnérabilité ?

On se propose, à travers ce travail de thèse, d'explorer à travers une revue orientée de la littérature les différentes définitions de la radiothérapie futile, notamment palliative. Puis on présentera une étude rétrospective portant sur les données de 3248 patients, afin de décrire les caractéristiques cliniques des malades décédés dans les deux mois qui ont suivi une irradiation. Nous étudierons ensuite les facteurs de risque de décès précoce chez les patients métastatiques traités par radiothérapie palliative et nous discuterons de l'utilité d'un score pronostique. Nous finirons par une réflexion sur la relation médecin-malade, en analysant les pistes de communication qui, associées aux facteurs pronostiques mis en évidence dans l'étude, devraient permettre de minimiser les traitements futiles et d'améliorer la prise en charge des patients cancéreux en fin de vie.

ARTICLE 1

FUTILE RADIATION THERAPY: DEFINITION IN CURATIVE AND PALLIATIVE CARE

ABSTRACT / RÉSUMÉ

La radiothérapie à visée symptomatique des lésions métastatiques concerne un patient irradié sur trois. Il s'agit d'un traitement efficace et bien toléré, mais non dépourvu d'inconvénients et dont l'effet clinique peut parfois n'apparaître que quatre à huit semaines après les séances; certains patients risquent donc de ne pas bénéficier d'une telle irradiation, en général parce qu'ils ne la supporteront pas jusqu'à son terme ou qu'ils décéderont avant d'en ressentir les effets positifs; c'est le concept de la radiothérapie futile.

Par analogie, on peut également qualifier de radiothérapie futile un traitement à visée curative, mais choisi et appliqué de manière tellement sous-optimale que cela risque d'impacter son objectif, à savoir l'amélioration de la survie du patient. En pratique, il s'agit le plus souvent d'arrêts en court d'irradiation, pour des raisons qui peuvent être liées au patient (comorbidité décompensée, retrait de consentement…), au traitement lui-même (fractionnement ou dose inadaptés, volume cible trop étendu ou mal situé, mauvaise gestion des effets secondaires aigus…) ou encore à la progression non anticipée du cancer. La futilité ne vient pas de l'inefficacité elle-même, mais du fait que cette inefficacité aurait dû être anticipée et évitée.

Le raisonnement est semblable pour les traitements palliatifs : la radiothérapie futile est celle qui n'a pas la possibilité d'attendre son but, en l'occurrence le soulagement des symptômes. Mais à la différence des curatifs, une majorité des patients palliatifs sont exposés à une inefficacité insuffisante du traitement parce qu'ils décèdent trop rapidement, soit pendant la radiothérapie, soit avant qu'elle ait pu agir (dans les deux mois).

La caractérisation de ces patients reste cependant difficile: la littérature scientifique ne propose que peu de données prospectives solides sur la radiothérapie palliative ou les interruptions prématurées des radiothérapies curatives. Même pour les localisations plus étudiées que sont les métastases osseuses et cérébrales, de nombreuses incertitudes demeurent. Les guidelines

sont peu suivies, souvent pour des raisons liées aux médecins (méfiance vis-à-vis des séances uniques pour les lésions osseuses, ou de l'irradiation cérébrale en totalité pour les patients les plus fragiles…). Cette hétérogénéité de prescription est également liée au fait que les praticiens sont mauvais juges du pronostic des patients; les médecins ont tendance à surévaluer la survie des malades palliatifs, ce qui les rend plus enclins à prescrire des traitements qui s'avéreront inadaptés. Il ne s'agit donc pas seulement de savoir qui traiter ou non, mais aussi comment les traiter (protocoles hypofractionnés?) et quand les traiter (balance entre bénéfice à court terme et risque à long terme en cas d'espérance de vie plus importante).

La sélection du traitement adapté à chaque patient est un problème complexe, influencé par de nombreux paramètres souvent intriqués. Le cancer primitif, le nombre et la localisation des métastases, l'état général du malade représentent autant d'indicateurs potentiels de fragilité et donc de risque de futilité, mais ils ne sont clairement pas suffisants ; pour appréhender pleinement les risques de traitement inadéquat, il paraît indispensable de compléter ces éléments cliniques et objectifs par une gestion appropriée des biais et préoccupations du médecin comme de ceux du patient.

Futile radiation therapy: definition in curative and palliative care

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INTRODUCTION

Radiation therapy (RT) is a pivotal treatment of malignant neoplasms at every stage of evolution, including symptomatic treatments in palliative care. In France, out of 216400 patients treated with RT in 2017, 20% were referred for metastases irradiation,[1, 2] a proportion that reach up to 30-50% in some centers across the world.[3, 4] Palliative RT is indeed an efficient and cost-effective treatment[3, 5, 6], most of the time quite well-tolerated even for fragile patients near end of life[4, 7].

However, palliative RT is not without downsides: a majority of prescribed courses implies several daily RT sessions, which can be difficult to manage for patients with poor global status or presenting severe pain that may be worsened by iterative transports[8] and repetitive immobilizations necessary to deliver the treatment.[9] Moreover, even palliative protocols, downgraded to obtain symptomatic improvement with the lowest possible dose to minimize toxicities, might provoke some acute side effects such as pain flare[10] or worsening of neurological symptoms[11]. All of these drawbacks have consequences for the patient's quality of life, and even if they are more often mild and present only for a small amount of time, when concerning a palliative patient in their last weeks of life, that it might still represent an intolerable impact[12]. Finally, as effective as palliative RT might be, most patients experienced symptomatic improvement only 4 to 6 weeks after treatment[13, 14]. Hence the relation with futile medical care: if a patient referred for palliative irradiation dies in the month following the treatment, there is a strong probability that they had to endure all downsides of RT without benefiting from symptom relief.

Another issue concerning palliative RT is that, despite this field representing a third of RT treatments, there is a surprising lack of strong, prospective clinical studies evaluating its modalities.[11, 15] Most of the references quoted in this article are reviews, retrospective

monocentric studies, or prospective studies on small monocentric samples. Pre-clinical data are also remarkably scarce when compared to the number of publications concerning curative RT.[15] Therefore, persistent uncertainties remain concerning the disease itself (what is the correlation between cancer growth and the intensity of the symptom?) as well as the clinical outcome for the patient: how to predict survival after palliative RT, and make the difference between short and long survivors? How long after treatment will the patient show some symptom improvement, or on the contrary some worsening of their condition? How to adapt the treatment (dose, fraction, schedule) to those surmises and to evade the risk of futile treatment?

DEFINITION OF A FUTILE TREATMENT: THE CASE OF CURATIVE RADIOTHERAPY

Before addressing the question of futile palliative RT, it seems important to give a precise definition of what we mean with "futile treatment". Authors have already established that it was a concept quite hard to define, depending on a lot of variables not only physician-related but also patient- and family-related[16, 17]. All in all, other papers on this subject seem to converge around the concept of futility as "an intervention that is unlikely to produce any significant benefit towards the patient". So to establish the futility of a treatment, one must begin with a clear definition of this treatment and what benefit it is supposed to produce.

Curative RT is easily defined as "aimed to cure", i.e. as a treatment characterized by its results. But we propose another point of view: qualifying a treatment as curative when it "aims to improve survival". This definition has the advantage of depending upon treatment's objective as decided at the beginning of RT, without prejudging of the outcome. The treatment is not considered in terms of results, but through its intent.

It clarifies the situation of some ambiguous status. For example, oligometastatic diseases, i.e. between 1 and 5 metastases potentially accessible to local treatments[18, 19], are clearly treated with curative intent despite corresponding to an advanced stage of cancer. Patients with locally very aggressive tumors such as glioblastoma are also treated in curative intent[20]: even if the efficiency of those treatments is currently quite unsatisfying and they are often sanctioned by a short lifespan, it remains curative because it aimed to prolong this lifespan – and maybe it did, compared to the natural evolution of the tumor.

Therefore, futility of a curative treatment doesn't come from a bad outcome in itself, it comes from a bad outcome that should have been anticipated at the referral, when the curative intent was chosen: if the treatment doesn't even have the chance to improve survival, then it is futile and an alternative should have been considered. For RT, this would be synonym of an interruption of the treatment course before reaching the prescribed dose: the patient is then exposed to the risk of not benefiting from the treatment.

Interruption of RT can be related to multiple causes, sometime simultaneous. There are some cancer related explanations: the tumor might evolve faster than expected, metastases might be discovered during RT… Treatment is then futile if the stage of the disease wasn't accurately determined at the beginning of the RT, or if the delay before treatment was too long. Other causes of interruption might be related to the treatment itself, most of the time because of acute side effects. In this case, futility comes from a potential poor follow-up, or a lack of supportive care. And at last, there might be some patient-related causes, e.g. comorbidity aggravated by the treatment, or the decision to stop the RT against medical advice; in this last situation, the futility is correlated to a potential communication issue (why did the patient agreed to the treatment to begin with and then changed their mind?).[7]

One might notice two particularities of all those justifications. The first is that they all become a manifestation of futility only depending on circumstances: if the disease progresses during

treatment when every surveillance protocol, every delay was respected, then there is no futility, because the interruption is an accident which couldn't be anticipated. The second particularity of these potential causes of futility is that they all are peripherical to the treatment itself. The indication of curative RT is not contested, it's its poor application that makes it futile.

PALLIATIVE RADIOTHERAPY

The problem is a little bit different for palliative RT, but it follows the same logic. If the definition of curative RT is "aiming for an improvement of survival", palliative RT would then be the opposite, i.e. "aiming for symptomatic relief" without searching to influence survival. A futile palliative RT would then be one which didn't even have the chance to improve patients' symptoms or quality of life. [21]

Despite the lack of prospective data concerning palliative RT, it is good to notice that the interest of specialized and referring physicians for this field seemed to expand in the last decade. The number of publications concerning re-treatment and palliative RT increased significantly[15] and recent national and international guidelines were proposed, most notably for bone[22] and brain metastases[23, 24]. We therefore dispose of quite recent data to discuss the objective of palliative RT, in order to understand how this goal can be missed in a futile way.

Main applications and corresponding types of futility

Bone metastases

Bones are the more frequent metastatic localization for solid cancers, they may concern up to two thirds of patients.[6] Metastases are more often localized in the rachis, source of rebel pain and of pathological fractures with or without neurologic compromise, which alters significantly the patient's quality of life[4]. The therapeutic options, apart from RT, include systemic treatments

(analgesics, bisphosphonates), minimally invasive intervention such as vertebroplasty or cementoplasty, or orthopedic surgery (e.g. laminectomy). Radiotherapy remains the most commonly used,[25] certainly because it presents an advantageous association between remarkable efficiency (up to 70% or 80% of patients with pain improvement) and very few acute side effects apart from potential pain flare[10] – and even then, this complication is quite manageable thanks to concomitant treatment with dexamethasone.

If the interest of palliative RT for bone metastases is known and widely accepted, technical modalities of this treatment are the source of an important controversy opposing long courses RT (40.5 Gy in 3 weeks, 30 Gy in two weeks) and short courses RT (20 Gy or 15 Gy in one week), or even a unique fraction (8 Gy x1). Three successive extensive reviews (Chow, 2007[26], update of Wu, 2003[27] and Sze, 2003[28]) established that 1) a single fraction is as effective as longer courses to improve bone pain, 2) the re-treatment rate is higher in short treatments (but maybe because radiation oncologists fear less toxicities with re-irradiation after a single fraction), 3) there is a trend for more pathological fracture with shorter treatments, but nothing significant. Data are lacking concerning quality of life, but all in all, at least for fragile patients with a poor global status and a short lifespan, single fraction RT seems an optimal treatment choice.

Concerning futile RT, we might notice two interesting parameters in those data: first, 54% of patients with complete pain relief experimented recurrence of pain at the treated site. This frequent occurrence cannot be qualified as a sign of futile treatment; not only the patient did benefit from the RT, even momentarily, but thanks to modern RT technics, the increasing possibilities of re-treatment make a symptom recurrence very unlikely to be related with a bad initial treatment choice. The second finding to notice is that in the RTOG survey conducted by Tong et al., 50% of patients who benefited of some symptomatic relief did so more than four weeks after RT, and the median delay before pain improvement was 12 weeks. [13]

So, if recurrence of pain for long survivors is not a criteria of futile RT, a patient's death in the first 12 weeks after treatment and even more in the first 4 weeks means that this patient has at least a 50% chance of not experimenting RT's clinical effect. Therefore, death within 4 and 12 weeks after palliative RT for bone metastasis are strong indicators of futility.

Furthermore, another point we might mention is the well investigated reluctance of radiation oncologists to prescribe single fraction treatments.[25] Most of the time, when asked about their justifications, clinicians mention the fear of late side effects after delivering a single more important dose, a fear that was never confirmed by research data.[28] The physician withholding a simpler, shorter treatment because of a personal belief is also a type of bias introducing a risk of futility, because this reasoning (true or false) as nothing to do with the patient, it's not adapted to the individual; by prolonging the RT course, the physician take a stronger risk of treatment interruption (because of fatigue related to transports, because of the pain caused by the mandatory immobilization during RT sessions).

Brain metastases

Second metastatic site to be treated with RT[11], the brain is also a good example of potential futile treatment. We will not talk in length about stereotactic brain RT, which might be at the limit with treatments of oligometastatic diseases, as it is currently proposed if there are less than 6 metastases, inferior to 30mm and in a context of controlled extracranial disease.[23]

A more eloquent case of potentially futile RT is the whole brain radiation therapy (WBRT). Indeed, ever since a 1971 study demonstrated a very modest clinical gain of WBRT plus steroids versus steroids alone[29], the use of this technique for palliative management of brain metastases has been subject to controversy: not only there are some doubts upon its efficiency for patients with poor global status compared to best supportive care alone,[11] but some authors are preoccupied by a potential neurocognitive toxicity appearing 3 to 4 months after WBRT[30–

[32] and impacting the quality of life of longer survivors[33]. Moreover, as it's the case for bone metastases, symptomatic improvement might take 4 to 8 weeks after RT to be effective[34]. Consequently, WBRT is not recommended for patients with a very poor prognosis, usually defined by an expected survival inferior to 3 months[23, 35].

However, research data reveal that there is a huge difference between individual survivals, even amongst populations with the same primary disease: medians of survival stretch from 2 to 9 months for patients with melanoma, from 2 to 14 months for small cell tumour and adenocarcinoma of the lung, from 3 to 30 months for breast cancer[36]. There is therefore an important need of tool to evaluate the patient's survival in order to optimize the treatment and know when to choose shorter RT courses (4 Gy x 5), to aim for a quick response for patients with limited lifespan[23, 35], or rather a longer RT course (3 Gy x 10, 2.5 Gy x 15) which might provoke less late toxicities for longer survivors.[24, 30]

However, physicians do not perform well when trying to predict the outcome of patients with extensive cancer,[37–39] they clearly tend to overestimate survival [40, 41] and therefore to obtain the opposite effect of the one intended, i.e. prescribing a futile treatment. Then this is the place of prognostic scores. Based upon observed clinical data, they suggest probabilities of survival depending of variables related to the patient and the disease. As a simple tool helping to make some difficult decisions, they became quite popular in the last twenty years[42]. For the WBRT alone, we may mention the Recursive Partitioning Analysis (RPA) score[43], or the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA)[44], now currently used as decision tools in most guidelines.[23, 35] There is also an important literature dedicated to update these existent scores, validating their internal or external value, exploring some of their identified prognostic factors such as extracranial metastases…[45, 46]

Of course, all those scores don't share the same accuracy, they have different advantages and weaknesses, are sometime very specific and useful only to a small part of the population… All

in all, they are interesting tools, but their results are merely indicative and must be interpreted with caution to not, once again, decide for a palliative RT based on criteria that represent only an incomplete summary of the patient's unique and peculiar situation.

Symptomatic epiduritis

Radiotherapy is the most common treatment for metastatic epidural spinal cord compression (MESCC), which may impact 2.5% to 5% of patients in the last two years of their disease and concern every major cancer (myeloma, prostate, breast, lung, gastro-intestinal primaries).[47]

A majority of patients with MESCC (60% to 85%) present some motor impairment at the diagnosis, however only 10% to 15% undergo decompressive surgery, with no clear benefit upon motor function.[48] Palliative RT alone is efficient for pain control, but it has only moderate effect on neurological deficit: only 20% of those patients get better after RT[48], and they are usually the ones with a slower installation of motor symptoms (more than 14 days before RT)[49]. Yet most patients not walking at referral won't walk again.[50]

This outcome is not modified by RT protocol: long courses (3 Gy x 10) and split-courses (5 Gy × 3 then 3 Gy × 5) are as efficient as short courses (4 Gy x 5, 8 Gy x 2 or even 8 Gy x 1)[50–52]. Some wondered about the interest of long course for patients with longer life expectancy (> 6 months) in order to improve bone reinforcement and facilitate the dosimetry of re-treatments[53], but more recent data indicates that with modern radiotherapy technics, short courses do not impair re-treatment, and that longer courses do not significantly modify the bone density related to remineralization[52].

Therefore, when considering palliative RT for a patient with MESCC near end of life, the physicians should ask themselves 1) what they are expecting from this treatment (if the patient present a brutal and total motor impairment with little to no pain, RT might not be the best

solution); 2) if they chose to treat, consider a shorter protocol, which would be as efficient and better tolerated whatever the patient's lifespan might be.

Furthermore, in this situation, we might signal another physician-related risk factor of futile care: for a lot of different reasons, doctors are usually quite reluctant to turn down a patient demanding for a treatment[54]. Interestingly, research data demonstrate that clinicians are quite self-conscious about the fact that this attitude might provoke some futile medical care[55]. This illustrate why prognostic scores are not enough to predict a patient outcome: understanding the guidelines, knowing about an "objective" reality, does not necessarily mean that physicians are able to distant themselves from an "inappropriate" emotional response.

Other palliative indications

Visceral metastases

Another major cause of referral for palliative RT is obstructive and/or bleeding related to a visceral tumoral localization, more often in the chest (lung, neck or esophagus cancer)[56] , in the gastro-intestinal system or in the pelvis (gynecologic, genito-urinary)[5]. Palliative RT is also quite effective on these targets, especially for controlling low-volume hemoptysis (79% of patients with improvement)[57]; results for dyspnea and cough related to an obstructive lung tumor are less satisfying (39%)[58]. However, those values must be interpreted with caution, as visceral localizations are less documented and studied than bone and brain metastases and protocols are even more diverse. Split-course RT[59] and brachytherapy[56] might be therapeutic options.

Non-metastatic palliative patients

The non-metastatic patients referred for palliative RT represent a small population (usually around 15% of palliative patients[60]) ineligible to a curative treatment, either for reasons related

to cancer (locally advanced, or in a localization inaccessible to an ablative treatment without debilitating side effects) or related to the patient (severe comorbidity, poor global status, refusal of curative treatment…). It may concern virtually any cancer and, when symptomatic, causes mainly pain, bleeding, or obstructive symptoms such as dyspnea.[58] Overall, palliative RT is very efficient on symptomatic tumors, with a decrease of symptoms for 60% to 80% of patients.[58, 61–63] But there are very few data regarding evaluation of different RT protocols and late toxicities developed by the few long survivors.

Elderly population

Given that the median age for cancer diagnostic is between 60 and 69 years old, elderly patients form an important proportion of patients (40% over 70 years old). They are more likely to develop metastatic diseases and often display more severe symptoms, yet they are often undertreated when compared to younger patients with same cancer at the same stage. [64, 65] Although, research data are consistent upon the fact that the age in itself doesn't impact upon palliative RT tolerance, nor does it reduce its efficiency[66], even for patients over 90 years old[67]. The worse survival and treatment response often observed in this population are certainly more related to poor global status and comorbidity than to the age in itself. Therefore, Nieder et al.[66] suggest than patients older than 80 years old should be treated following the same criteria that younger ones as long as their ECOG-PS is 0 to 3; as for the others, more fragile ones, caution in treatment choice should be applied and an alternative to palliative RT should be considered.

CONCLUSION

Through this review of different types of futile RT, we defined a futile treatment as one that didn't meet the circumstances necessary to its optimal execution, in a way that could have been anticipated. For curative RT "aimed to improve survival" as for palliative RT "aimed to improve symptoms", it meant an interruption for patient-related, treatment related or cancer-related causes, with the risk for the patient of not experiencing the expected effect on their survival or on their symptoms. More often, for palliative RT, it means an interruption of the course for poor global status, for cancer-related reason, or because of end of life.

We described three types of futility related to the treatment itself: treating the wrong patient (e.g. a patient with poor global status and severe motor impairment from epiduritis), treating at the wrong time (too early for WBRT and risking late side effects for long survivors, too late for occlusive tumor and risking death before the manifestation of any clinical effect) and treating with the wrong manner (longer protocol without any rational). Patient-related and physician-related factors should be added to those treatment-related factors to obtain a complete landscape of the difficulties to define, recognize and avoid futile RT, despite the more objective help of some prognostic scores.

REFERENCES

1. Les cancers en France en 2018 - L'essentiel des faits et chiffres (édition 2019) [Internet], 2019Available from: https://www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/Les-cancers-en-France-en-2018-L-essentiel-des-faits-et-chiffres-edition-2019

2. Nombre de patients traités par radiothérapie en fonction de la localisation [Internet], 2019Available from: http://lesdonnees.e-cancer.fr/Themes/Soins/La-radiotherapie/L-activite-et-les-techniques-de-traitement/La-radiotherapie-externe2/Nombre-de-patients-traites-par-radiotherapie-en-fonction-de-la-localisation#graphique

3. Samant R, Tucker T: How should we describe the benefits of palliative radiotherapy? Curr Oncol 13:230–234, 2006

4. Van Oorschot B, Rades D, Schulze W, et al: Palliative Radiotherapy—New Approaches. Seminars in Oncology 38:443–449, 2011

5. Konski A: Radiotherapy is a cost-effective palliative treatment for patients with bone metastasis from prostate cancer. International Journal of Radiation Oncology • Biology • Physics 60:1373–1378, 2004

6. Le Fèvre C, Menoux I, Pin Y, et al: Coût de la radiothérapie des métastases osseuses en France : étude rétrospective monocentrique. Cancer/Radiothérapie 23:1–9, 2019

7. Clément-Zhao A, Luu M, Bibault J-E, et al: Effective delivery of palliative radiotherapy: A prospective study. Cancer/Radiothérapie 23:365–369, 2019

8. Hubbard G, Maguire R, Kidd L, et al: Patient views of transport for cancer treatment. European Journal of Oncology Nursing 10:391–395, 2006

9. Haaser T: Prise en charge des patients en fin de vie en service de radiothérapie [Internet], in Fins de vie, éthique et société. Toulouse, ERES, 2016, pp 281–285Available from: https://www.cairn.info/fins-de-vie-ethique-et-societe--9782749251905-p-281.htm

10. Hird A, Chow E, Zhang L, et al: Determining the Incidence of Pain Flare Following Palliative Radiotherapy for Symptomatic Bone Metastases: Results From Three Canadian Cancer Centers. International Journal of Radiation Oncology*Biology*Physics 75:193–197, 2009

11. Mulvenna P, Nankivell M, Barton R, et al: Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. The Lancet 388:2004–2014, 2016

12. Timmermans LM, van der Maazen RWM, Verhaak CM, et al: Patient participation in discussing palliative radiotherapy. Patient Education and Counseling 57:53–61, 2005

13. Tong D, Gillick L, Hendrickson FR: The palliation of symptomatic osseous metastases final results of the study by the radiation therapy oncology group. Cancer 50:893–899, 1982

14. Spencer K, Morris E, Dugdale E, et al: 30 day mortality in adult palliative radiotherapy – A retrospective population based study of 14,972 treatment episodes. Radiotherapy and Oncology 115:264–271, 2015

15. Nieder C, Andratschke NH, Grosu AL: Increasing frequency of reirradiation studies in radiation oncology: systematic review of highly cited articles. Am J Cancer Res 3:152–158, 2013

16. Rodriguez KL, Young AJ: Perceptions of patients on the utility or futility of end-of-life treatment. J Med Ethics 32:444–449, 2006

17. Saettele A, Kras J: Current Attitudes of Anesthesiologists towards Medically Futile Care. Open Journal of Anesthesiology 3:207–213, 2013

18. Hellman S, Weichselbaum RR: Oligometastases. JCO 13:8–10, 1995

19. Kissel M, Helou J, Thariat J: Nouvelles définitions de la maladie oligométastatique et nouveaux concepts de prise en charge globale de la maladie métastatique. Bulletin du Cancer 105:696–706, 2018

20. L. Feuvret, D. Antoni, J. Biau, et al: Référentiels d'irradiation des gliomes. Cancer / Radiothérapie 4982:S1, 2016

21. Westhoff PG, de Graeff A, Monninkhof EM, et al: Quality of Life in Relation to Pain Response to Radiation Therapy for Painful Bone Metastases. International Journal of Radiation Oncology*Biology*Physics 93:694–701, 2015

22. Thureau S, Vieillard M-H, Supiot S, et al: Radiothérapie des métastases osseuses. Cancer/Radiothérapie 20:S227–S234, 2016

23. Le Rhun É, Dhermain F, Noël G, et al: Recommandations de l'Anocef pour la prise en charge des métastases cérébrales. Cancer/Radiothérapie 19:66–71, 2015

24. Latorzeff I, Antoni D, Gaudaire-Josset S, et al: [Radiotherapy for brain metastases]. Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique 20 Suppl:S80-7, 2016

25. Fairchild A, Barnes E, Ghosh S, et al: International Patterns of Practice in Palliative Radiotherapy for Painful Bone Metastases: Evidence-Based Practice? International Journal of Radiation Oncology*Biology*Physics 75:1501–1510, 2009

26. Chow E, Harris K, Fan G, et al: Palliative Radiotherapy Trials for Bone Metastases: A Systematic Review. JCO 25:1423–1436, 2007

27. Wu JS-Y, Wong R, Johnston M, et al: Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. International Journal of Radiation Oncology*Biology*Physics 55:594–605, 2003

28. Sze WM, Shelley MD, Held I, et al: Palliation of Metastatic Bone Pain: Single Fraction versus Multifraction Radiotherapy – A Systematic Review of Randomised Trials. Clinical Oncology 15:345–352, 2003

29. Horton J, Baxter DH, Olson KB: The management of mestastases to the brain by irradiation and corticosteroids. American Journal of Roentgenology 111:334–336, 1971

30. Aoyama H, Tago M, Kato N, et al: Neurocognitive Function of Patients with Brain Metastasis Who Received Either Whole Brain Radiotherapy Plus Stereotactic Radiosurgery or Radiosurgery Alone. International Journal of Radiation Oncology*Biology*Physics 68:1388–1395, 2007

31. Chang EL, Wefel JS, Hess KR, et al: Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. The Lancet Oncology 10:1037–1044, 2009

32. Brown PD, Jaeckle K, Ballman KV, et al: Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical TrialSRS With or Without WBRT and Cognitive Function in Patients With Brain MetastasesSRS With or Without WBRT and Cognitive Function in Patients With Brain Metastases. JAMA 316:401–409, 2016

33. Soffietti R, Kocher M, Abacioglu UM, et al: A European Organisation for Research and Treatment of Cancer Phase III Trial of Adjuvant Whole-Brain Radiotherapy Versus Observation in Patients With One to Three Brain Metastases From Solid Tumors After Surgical Resection or Radiosurgery: Quality-of-Life Results. JCO 31:65–72, 2012

34. Sundaresan P, Yeghiaian-Alvandi R, Gebski V: Prognostic index to identify patients who may not benefit from whole brain radiotherapy for multiple brain metastases from lung cancer. Journal of Medical Imaging and Radiation Oncology 54:69–75, 2010

35. Tsao MN, Rades D, Wirth A, et al: Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline. Practical Radiation Oncology 2:210–225, 2012

36. Cagney DN, Martin AM, Catalano PJ, et al: Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. Neuro-Oncology 19:1511–1521, 2017

37. Bruera E, Miller MJ, Kuehn N, et al: Estimate of survival of patients admitted to a Palliative Care Unit: A prospective study. Journal of Pain and Symptom Management 7:82–86, 1992

38. Glare P, Virik K, Jones M, et al: A systematic review of physicians' survival predictions in terminally ill cancer patients. BMJ 327:195, 2003

39. Tseng YD, Krishnan MS, Sullivan AJ, et al: How Radiation Oncologists Evaluate and Incorporate Life Expectancy Estimates Into the Treatment of Palliative Cancer Patients: A Survey-Based Study. International Journal of Radiation Oncology*Biology*Physics 87:471–478, 2013

40. Kondziolka D, Parry, P. V., L. Dade Lunsford, et al: The accuracy of predicting survival in individual patients with cancer. Journal of Neurosurgery JNS 120:24–30, 2014

41. Barnes EA, Chow E, Tsao MN, et al: Physician Expectations of Treatment Outcomes for Patients With Brain Metastases Referred for Whole Brain Radiotherapy. International Journal of Radiation Oncology • Biology • Physics 76:187–192, 2010

42. Taillibert S, Le Rhun É: Épidémiologie des lésions métastatiques cérébrales. Cancer/Radiothérapie 19:3–9, 2015

43. Gaspar L, Scott C, Rotman M, et al: Recursive partitioning analysis (RPA) of prognostic factors in three radiation therapy oncology group (RTOG) brain metastases trials. International Journal of Radiation Oncology • Biology • Physics 37:745–751, 1997

44. Sperduto PW, Kased N, Roberge D, et al: Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol 30:419–425, 2012

45. Rades D, Gerdan L, Segedin B, et al: Brain metastasis. Strahlenther Onkol 189:996–1000, 2013

46. Gerdan L, Segedin B, Nagy V, et al: Brain metastasis from non-small cell lung cancer (NSCLC). Strahlenther Onkol 190:64–67, 2014

47. Prasad D, Schiff D: Malignant spinal-cord compression. The Lancet Oncology 6:15–24, 2005

48. Rades D, Abrahm JL: The role of radiotherapy for metastatic epidural spinal cord compression. Nature Reviews Clinical Oncology 7:590–598, 2010

49. Rades D, Heidenreich F, Karstens JH: Final results of a prospective study of the prognostic value of the time to develop motor deficits before irradiation in metastatic spinal cord compression. International Journal of Radiation Oncology*Biology*Physics 53:975–979, 2002

50. Maranzano E, Trippa F, Casale M, et al: 8 Gy single-dose radiotherapy is effective in metastatic spinal cord compression: Results of a phase III randomized multicentre Italian trial. Radiotherapy and Oncology 93:174–179, 2009

51. Maranzano E, Bellavita R, Rossi R, et al: Short-Course Versus Split-Course Radiotherapy in Metastatic Spinal Cord Compression: Results of a Phase III, Randomized, Multicenter Trial. JCO 23:3358–3365, 2005

52. Sprave T, Hees K, Bruckner T, et al: The influence of fractionated radiotherapy on the stability of spinal bone metastases: a retrospective analysis from 1047 cases. Radiat Oncol 13:134–134, 2018

53. Koswig S, Budach V: Remineralization and pain relief in bone metastases after after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy). A prospective study. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft . [et al] 175:500–508, 1999

54. Kasman DL: When is medical treatment futile? A guide for students, residents, and physicians. J Gen Intern Med 19:1053–1056, 2004

55. Willmott L, White B, Gallois C, et al: Reasons doctors provide futile treatment at the end of life: a qualitative study. J Med Ethics 42:496, 2016

56. Shasha D, Harrison LB: The role of brachytherapy for palliation. Seminars in Radiation Oncology 10:222–239, 2000

57. Gaito S, Hughes C, Woolf D, et al: Radiotherapy in the control of bleeding from primary and secondary lung tumours. Br J Hosp Med 80:211–215, 2019

58. Langendijk JA, ten Velde GPM, Aaronson NK, et al: Quality of life after palliative radiotherapy in non-small cell lung cancer: a prospective study. International Journal of Radiation Oncology*Biology*Physics 47:149–155, 2000

59. Kancherla KN, Oksuz DC, Prestwich RJD, et al: The Role of Split-course Hypofractionated Palliative Radiotherapy in Head and Neck Cancer. Clinical Oncology 23:141–148, 2011

60. Van Oorschot B, Schuler M, Simon A, et al: Patterns of Care and Course of Symptoms in Palliative Radiotherapy. Strahlentherapie und Onkologie 187:461, 2011

61. Cameron MG, Kersten C, Vistad I, et al: Palliative pelvic radiotherapy of symptomatic incurable rectal cancer - a systematic review. Acta Oncol 53:164–173, 2014

62. Cameron MG, Kersten C, Guren MG, et al: Palliative pelvic radiotherapy of symptomatic incurable prostate cancer – A systematic review. Radiotherapy and Oncology 110:55–60, 2014

63. Tey J, Soon YY, Koh WY, et al: Palliative radiotherapy for gastric cancer: a systematic review and meta-analysis. Oncotarget 8:25797–25805, 2017

64. Ludbrook JJS, Truong PT, MacNeil MV, et al: Do age and comorbidity impact treatment allocation and outcomes in limited stage small-cell lung cancer? a community-based population analysis. International Journal of Radiation Oncology • Biology • Physics 55:1321–1330, 2003

65. Campos S, Presutti R, Zhang L, et al: Elderly Patients With Painful Bone Metastases Should be Offered Palliative Radiotherapy. International Journal of Radiation Oncology*Biology*Physics 76:1500–1506, 2010

66. Nieder C, Angelo K, Haukland E, et al: Survival After Palliative Radiotherapy in Geriatric Cancer Patients. Anticancer Research 34:6641–6645, 2014

67. Méry B, Rancoule C, Assouline A, et al: Efficacy and tolerance of thoracic radiotherapy in the oldest old patients: A case series56:163–166, 2019

ARTICLE 2

FUTILE RADIATION THERAPY:
CLINICAL CHARACTERISTICS OF 3248 PATIENTS
TREATED WITH CURATIVE OR PALLIATIVE RADIOTHERAPY
AND PROGNOSTIC FACTORS OF EARLY DEATH

ABSTRACT / RÉSUMÉ

Introduction

La radiothérapie (RT) futile, qui par son interruption ou sa prescription trop proche du décès du patient (moins de deux mois) n'apporte aucun bénéfice à ce dernier, correspond à une réalité quotidienne mais peu explorée par la littérature médicale. Cette étude se propose de décrire la population des patients concernés et d'établir les facteurs pronostiques de décès à court terme qui devraient faire reconsidérer la prescription de RT, notamment chez les malades adressés pour irradiation palliative à visée symptomatique.

Matériel & Méthode

Cette étude rétrospective monocentrique est basée sur les données cliniques de 3501 patients: caractéristiques individuelles (sexe, âge, Performance Status (PS), antécédent de radiothérapie, hospitalisation en cours, traitement systémique concomitant), de leur cancer (primitif, histologie, éventuels sites métastatiques) et de leur traitement (dose, fractionnement et durée de la radiothérapie, site traité, intention curative ou palliative, motif des RT palliatives (PRT), interruption prématurée). Nous avons effectué une analyse descriptive de cette population, en prêtant attention aux patients décédés à 7 jours, 30 jours et 60 jours de la fin de la RT. Puis nous avons procédé à une analyse de la survie. Pour les patients métastatiques en soins palliatifs (MD-PRT), nous avons recherché les facteurs pronostiques influençant la survie globale, puis la survie à 7 jours, à 30 jours, à 60 jours; nous avons ensuite proposé un score pronostique qualitatif évaluant le risque de ces patients de décéder à court terme.

Résultats

Sur les 3501 patients traités, 3248 ont été inclus. Parmi eux, 32.2% étaient à un stade métastatique (MD) et 32.1% adressés pour PRT. Le groupe MD-PRT concernait 28.6% des patients. Les médianes de survie mesurables étaient de 5.9 mois (MD) et 4.4 mois (PRT), elles étaient non atteintes par les patients curatifs ou non-métastatiques. Sept jours après la RT, 2.6%

des patients étaient décédés, puis 7.2% à 30 jours et 11.7% à 60 jours, dont une majorité de PRT (31.3%). Pour les patients MD-PRT, les facteurs de risque de décès dans les deux mois suivant la RT étaient un PS élevé (HR = 1.88 (1.66-2.12)), l'invasion métastatique de multiples sites anatomiques (HR = 1.11 (1.03-1.22)), des métastases cérébrales symptomatiques (HR = 1.58 (1.18-2.12)), un cancer primitif du pharynx (HR = 3.30 (1.04-10.46)) ou du système digestif (HR = 2.76 (1.48-5.41) pour l'œsophage, HR = 0.38 (0.19-0.79) pour les autres primitifs sauf rectum et canal anal). Les facteurs protecteurs étaient un cancer primitif du sein (HR = 0.48 (0.33-0.70)) ou de la prostaste (HR = 0.38 (0.19-0.79)), ainsi qu'un traitement de métastases cérébrales par RT en conditions stéréotaxiques (SRT) (HR = 0.58 (0.38-0.88)). En scores composites, une localisation tumorale médiastinale compressive était associée à une surmortalité alors que les patients avec un unique site métastatique ou avec des métastases cérébrales asymptomatiques et accessibles à une SRT présentaient un meilleur pronostic. Au final, notre score pronostique proposait en facteurs de risque un PS 3-4, au moins trois sites métastatiques, un primitif du pharyngo-larynx ou digestif (rectum excepté) et une lésion médiastinale compressive; en facteurs protecteurs, un PS 0-1, un unique site métastatique, un primitif mammaire ou prostatique et des métastases cérébrales asymptomatiques avec SRT.

Conclusion

Les patients décédés moins de deux mois après la RT et par conséquent exposés à un traitement potentiellement futile représentent près d'un tiers des patients palliatifs. Une forte valeur pronostique semble associée au PS et au nombre de sites métastatiques, ainsi qu'aux primitifs du pharyngo-larynx et digestifs (surmortalité) ou du sein et de la prostate (protecteurs). Des recherches complémentaires sont nécessaires pour établir le poids respectif de ces facteur de risque dans le décès précoce des malades, mais les tumeurs thoraciques compressives paraissent d'un pronostic particulièrement sombre et devraient faire questionner l'indication de RT symptomatique, ou au minimum faire privilégier des protocoles courts.

Futile radiation therapy: clinical characteristics of 3248 patients treated with curative or palliative radiotherapy and prognostic factors of early death

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INTRODUCTION

Futile radiotherapy (RT) is an unusual concept with very few echoes in literature, despite being pretty common in radiation therapy services. The exact definition varies with the curative or palliative intent of the treatment, but overall it characterizes RT courses which may not reach their full effect because they were not applied with the appropriate parameters to the appropriate patient. At its most extreme form, a futile RT is a form of futile medical care: it's the RT that "is unlikely to produce any significant benefit towards the patient", the RT should not have been done given data known when the patient was referred to the radiation oncologist.[1]

Therefore, in a curative setup, with a treatment aiming to improve overall survival or at least cancer specific survival, the futile RT is the one which does not impact the time of death because of a predicable alteration of its delivering (not anticipated clinical alteration, underestimated comorbidities, inadequate evaluation of cancer stage, poor management of acute side effects…). It does not cover the lack of clinical impact because of cancer progression (inefficiency) or because or stochastic delayed side effects (late toxicities), both of these phenomena being unpredictable at the beginning of the treatment. As a result, futility in curative RT is quite difficult to assess in a retrospective study, given the subtlety of clinical data and of their association that may hint the incomplete outcome of those treatments.

The problem is quite different for palliative RT, which typically does not aim to increase survival but to treat symptoms.[2] It may be applied in an exclusive palliative care setup as well as concomitantly to a systemic therapy aimed toward survival improvement, but overall, it concerns patients with a poorer outcome and a limited life expectancy. The question of futility is therefore simpler to define it concerns treatments that don't lessen symptoms because the patient dies before the expected clinical effect.

However, it is not so easy to determine if this symptomatic effect was reached or not before end of life. With a very few exceptions (most notably brain metastases[3]), the evaluation of palliative RT in literature rely mostly upon the rate of symptom improvement and quality of life evaluation[,2]. But those parameters are also quite complex to estimate, especially in a retrospective study: even when their evolution is not simply missing in patients' files (most of time because of poor follow-up), their diversity, from bone pain to neurological pain, from obstructive dyspnea to hemorrhage, make a unique and reproductible assessment tool impossible to compute.[4] Moreover, the severity of those symptoms is more often highly subjective and their evaluation differs from one physician to another, from one patient to another, and between physicians and patients.[5]

Therefore, our study proposed to focus not on symptom evaluation, but on overall survival. This choice may seem a paradox given the definition we discussed right above, yet it was based upon a simple fact concerning palliative RT: its delayed clinical effect. Indeed, there are quite consistent data indicating that symptomatic RT is effective only after a mean time of 4 to 6 weeks[6, 7]. So if a patient dies in the first two months after RT, there is a probability that they did not experienced the expected clinical relief. Even if this delay can be enough for RT to be effective for some patients to be relieved before their death, a significant part will still be treated for nothing, experiencing drawbacks of RT without the advantages. For these patients, it might be more appropriate to choose other types of palliative care, less costly in terms of transports and potential acute side effects (painful position during treatment, pain flare, worsening of neurological symptoms...).[8–10]

This study aimed to describe demographic data of curative and palliative population treated with RT, then to identify some prognostic factors of early death (in the two months) of metastatic patients which could help to avoid futile palliative RT.

MATERIAL AND METHODS

Study population

We retrospectively identified a cohort of consecutive patients treated between the 1st January 2012 and the 1st January 2015 in the Department of Radiation Oncology from the Centre Paul Strauss, Strasbourg, France.

We included every patient over 18 years old who had been treated at least partially by external radiotherapy for a malignant solid tumor, excluding hematological diseases (leukemia, lymphoma, myeloma), benign tumors (meningioma, pituitary adenoma…) and non-tumoral pathologies (Grave's orbitopathy…).

As we performed an intention-to-treat analysis, patients lost to follow-up in the first 12 months and patients with an incomplete treatment course were also included.

This monocentric retrospective study complies with the "reference methodology" MR004 adopted by the French Data Protection Authority (CNIL) and patients did not object to the use of their clinical data for the research purpose.

Clinical data

Patient-related data included sex, age, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), history of precedent radiotherapy treatment, concomitant chemotherapy (i.e. not interrupted during RT) or palliative chemotherapy (i.e. interrupted only when not compatible with RT). We noted if patients were hospitalized when referred to the radiation oncologist.

Disease-related data were the primary cancer site and histological type. If the patient presented with a metastatic disease, we collected the number of metastatic sites (i.e. different organs invaded) and their localizations.

Treatment-related data included RT technic (3-Dimensional Conformational Radiation Therapy (3D-CRT), Intensity Modulated Radiation Therapy (IMRT), Stereotactic Radiation Therapy (SRT)), RT duration, total dose, number of fractions and treated site. We classified the treatment's objective either as curative intent or as palliative intent, curative RT being "aimed to survival improvement" when palliative RT was "aimed toward symptoms control". When the patient was referred for palliative RT, we mentioned the targeted symptom (pain, hemorrhage, visceral compressive symptoms, local control (including asymptomatic epiduritis), asymptomatic or symptomatic brain metastases).

We also collected interruptions of treatment and their justification: patient's choice against medical advice, clinical degradation related to cancer (progression or treatment) or not, death related to cancer (progression or treatment) or not.

Data were then stratified by metastatic disease (MD) or non-metastatic disease (NMD), and by curative RT (CRT) or palliative RT (PRT) so we could define four groups of patients: metastatic and palliative (MD-PRT group), non-metastatic and palliative (NMD-PRT group), metastatic and curative (MD-CRT group) and non-metastatic and curative (NMD-CRT group).

Follow-up

Follow-up was recorded for all patients from the first consultation for radiotherapy planification to the patient death, or status at last news or at study endpoint (30th June 2019). When patients were referred to the radiotherapy service several times during the inclusion period, data were collected at the beginning of the latest treatment.

We were especially vigilant to minimize lost to follow-up patients in the first year after radiotherapy. When our service's data were lacking in this period, we updated follow-up by contacting patients' referring physician and/or their general practitioner.

Statistical analysis: descriptive analysis

Descriptive statistics were applied to the whole population, with stratification by metastatic status and treatment's objective. Deceased patients' characteristics were studied at 7 days, 30 days, 60 days, 6 months and at one year after the last delivered radiotherapy session.

Statistical analysis: survival analysis

Overall survival (OS) outcome was defined as the time between the last radiotherapy session and the death due to any cause. Corresponding survival curves and their 95% confidence intervals were estimated using the Kaplan Meier method and compared with the log-rank test. When tested for outliers (ROUP test with Q = 1%), both the MD and the PRT groups showed a significative and equivalent proportion of survival beyond a theoretical Gaussian distribution (respectively 179 out of 1047 (17.1%) and 179 out of 1041 (17.2%)). Those values corresponded to statistically long survivors, i.e. more than 32 months for those with metastatic disease and more than 20.4 months for the palliative RT group. Removing those patients as outliers didn't improve the results of normality tests (all negative, $p < 0.0001$). Given their clinical relevance, we therefore chose to keep the extreme values in the analysis.

Statistical analysis: prognostic factors

To look for prognostic factors influencing OS,[11, 12] we first used a univariate survival analysis with the Cox model[13] to select significant variables. We then looked for interaction between those variables' effect with a correlation test (the Farrar-Glauber multicollinearity test[14]). When there was a significant correlation between two variables, we discarded the one that we deemed to be less reproducible and less clinically relevant. The remaining variables were included in a multivariate Cox analysis. Only the significant ones were kept in a final stepwise regression, which allowed us to construct the best performing model with lower prediction error.

As we aimed to identify prognostic factors for early survival, we chose to apply this process to the part of the study's population with the worse OS, i.e. patients presenting with metastatic disease and referred for palliative RT (MD-PRT group). We then ran the same succession of analysis for patients of this same group deceased at 7 days, 30 days and 60 days after the end of radiotherapy.

Statistical analysis: control of prognostic factors

We grouped identified prognostic factors following same categories that we used for the data collection (patients' characteristics, primary type, metastatic sites, treated locations). Inside each category, we established Kaplan-Meier survival curves for patients presenting with prognostic factors, then compared their survival with the whole MD-PRT population. This analysis was done using log-rank tests, corrected for multiple comparisons with Holm- Šídák test[15].

Computer programs used

All statistical analysis was performed using R version 3.5.0 for MacOS X[16] (with packages tableone[17], survival[18], survminer[19], GGally[20], mctest[21], corrplot[22], ggplot2[23] and My.stepwise[24]) and GraphPad Prism version 8.2.0 for MacOS[25], with help from the GraphPad Statistic Guide[26].

RESULTS

Population distribution

We collected data for 3501 patients. Following exclusion criteria as presented in the study flow chart (Figure 1), we included 3248 patients in the analysis. Their characteristics are displayed in Table 1A.

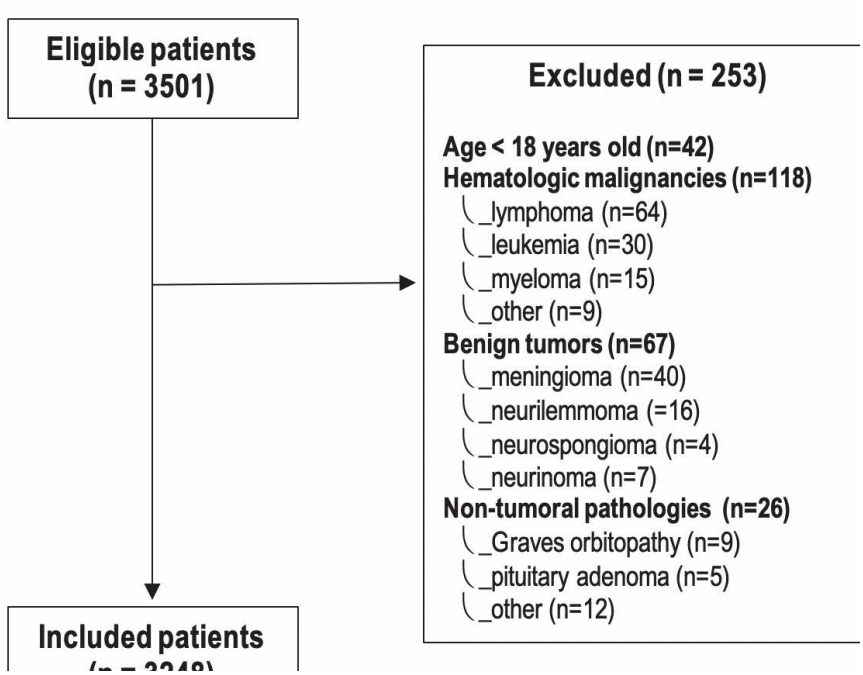

Figure 1: Study's population flowchart

Amongst those patients, 1047 (32.2%) presented a metastatic disease and 1041 (32.1%) were referred for PRT. Those groups overlapped widely, leaving only 118 (3.6%) MD-CRT and 112 (3.5%) NMD-PRT patients. Therefore, the majority of the population belonged in the MD-PRT group (929 patients, 28.6%) and in the NMD-CRT group (2089 patients, 64.3%) (Figure 2).

The median follow-up was 28 months (from 0 to 88.2 months). When stratified by metastatic status and treatment's objective, median follow-up ranged from 4.5 months (MD) to 42.6 months (NMD) and from 3.6 months (PRT) to 44.3 months (CRT). Lost to follow-up patients at one year represented only 5.5% of the overall population.

Patients' characteristics

In the whole population, there were slightly more women than men (57.6%), especially in the NMD (62.3%) and the CRT (62.6%) groups. The mean age was 63.2 years old (19 to 98).

A majority of patients had an ECOG-PS of 1 (40.5%), a proportion quite stable in every studied groups (from 35.5% to 43%). However, NMD and CRT patients displayed mostly a PS of 0 (44.4% and 46%), when more MD and PRT patients had a PS of 2 (28.6% and 30.9%).

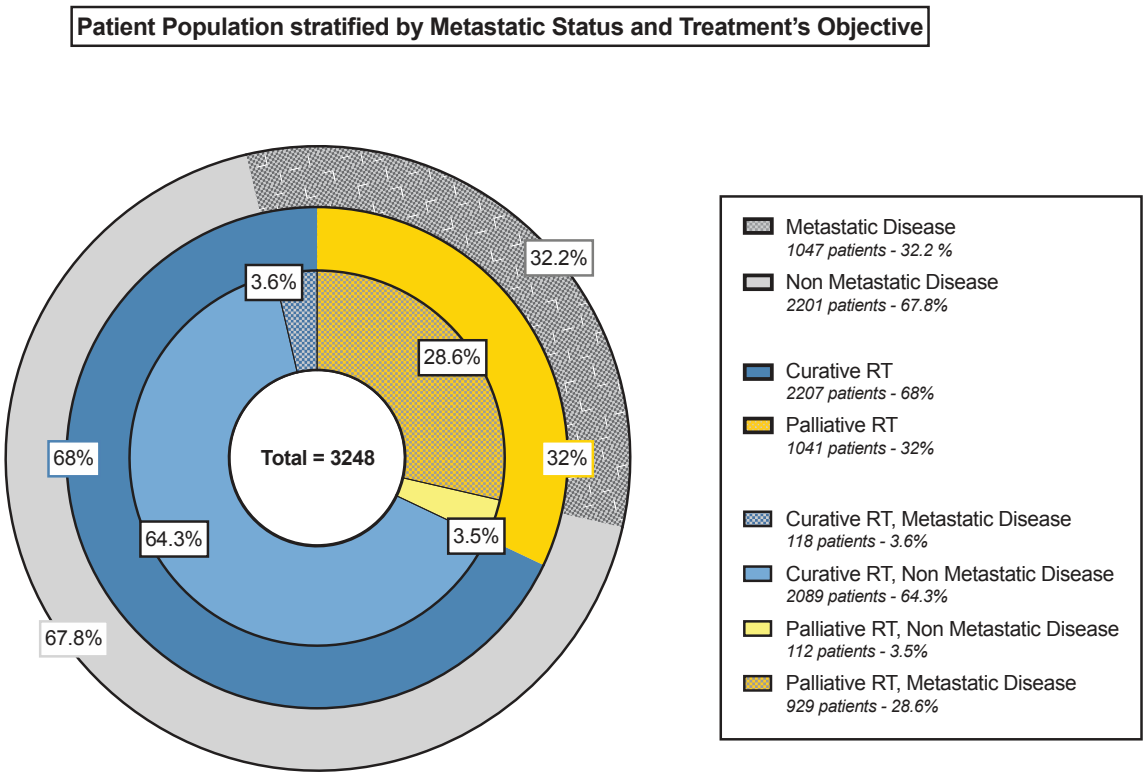

Figure 2: Patients' population stratified by metastatic status and treatment's objective

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One out of ten patients (10.9%) was hospitalized when referred for RT, with strong disparities depending upon the metastatic status (3.7% of NMD versus 26.1% of MD patients) and the treatment objective (2.3% of CRT versus 29.2% of PRT patients). The same observation could be made for prior radiotherapy treatment in patient's history: it concerned 23.1% of the whole population, but only 10.9% of NMD patients and up to 48.8% of MD ones.

Finally, concomitant or palliative systemic treatment concerned 30.6% of all patients, from 23.2% (CRT) to 46.4% (PRT).

Disease characteristics

Primary tumors repartition can be seen in Table 1B.

The most prevalent primary type was breast cancer, concerning 34.3% of the population. The second most frequent type was lung cancer (16.5%), followed by digestive primaries (11.9%), head and neck cancers (11.4%) and gynecological localizations (6.3%).

As for metastatic sites, the most frequent was the bone (16.8%), followed by the brain (14.1%), the lung (10.0%), the liver (7.9%) and the presence of distant pathological nodes (5.9%).

Treatments characteristics

Most patients were treated with 3D-CRT (69.4%).

As observed for primary tumors' characteristics, other treatment's aspects were significantly different between patients' subgroups: on average, NMD and CRT patients were treated with higher doses (respective mean doses of 55.6 Gy and 56.1 Gy), for a longer time (mean of 40.5 and 40.8 days) and mostly with normo-fractioned treatments (2.5 and 2.6 Gy/fr), whereas MD and PRT patients were treated with mean doses of respectively 28.2 and 29.6 Gy, during a mean of two weeks (12.1 and 12.8 days) with more important dose per fraction (5.4 and 5.6 Gy).

Concerning PRT, most patients were referred for symptoms control (69.3%), especially because of pain (25.9%) and neurological symptoms caused by brain metastases (19.9%). Other PRT patients were treated with an objective of local control (30.7%), half of the time because of a currently asymptomatic lesion (essentially brain metastases (17.7%) and epiduritis (2.8%)) (Figure 3).

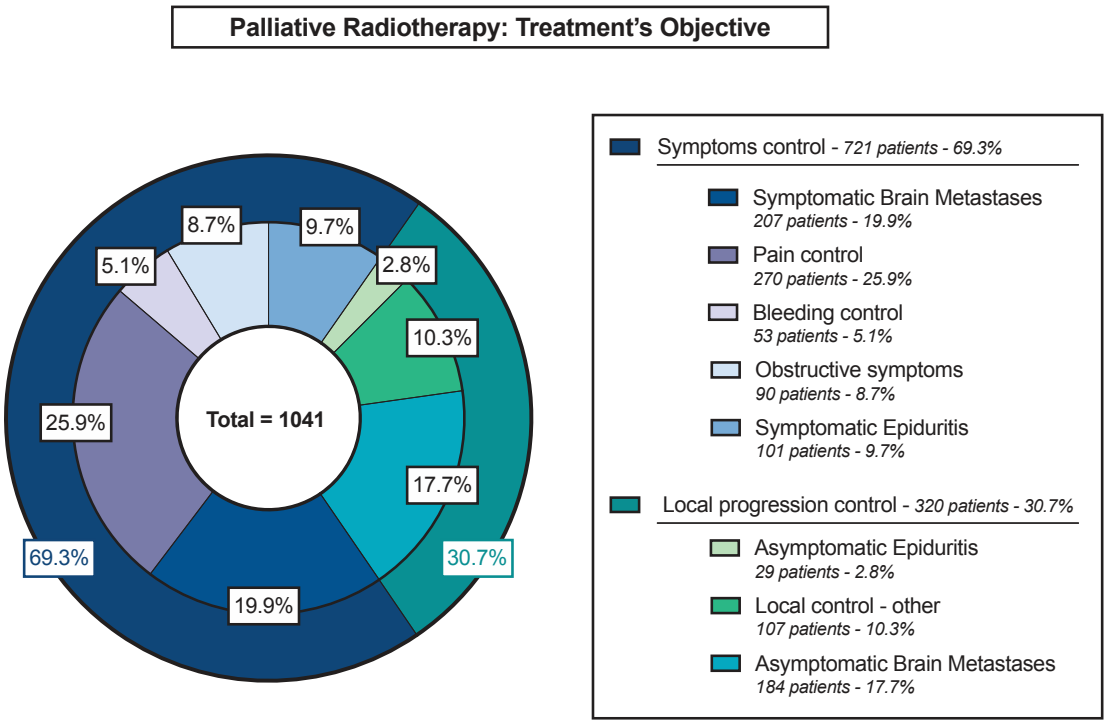


Figure 3: Palliative radiotherapy: treatment's objective

Interruption of RT

Out of 3248 patients, only 135 (4.2%) did not complete the RT course, including 88 PRT patients (65.2% of interrupted treatments, 8.5% of all PRT patients). As displayed in Figure 4, patients stopped RT predominantly because of a severe clinical degradation (45.9%) or because of death (36.3%). Most of the time, this outcome was related to cancer progression (50.4%) or to another clinical issue (23.7%). The third reason to stop the RT was patient's decision against medical advice, concerning 24 people (17.8%). Most of those voluntary interrupted treatments were in curative intend (54.2%) for non-metastatic patients (66.7%). Only 11 interruptions (8.1%) were the consequence of treatment's toxicity, including two deaths (a septic choc during concomitant radio-chemotherapy and a cerebral herniation after the second session of whole brain RT).

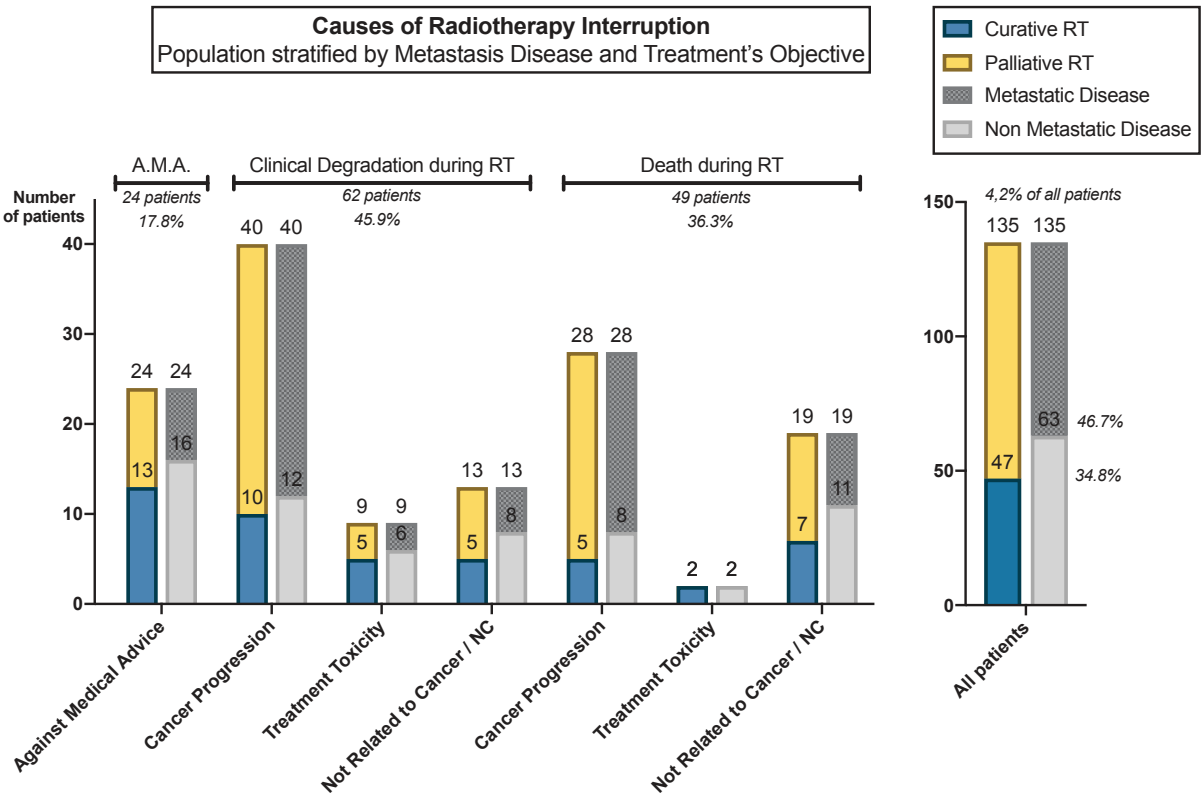
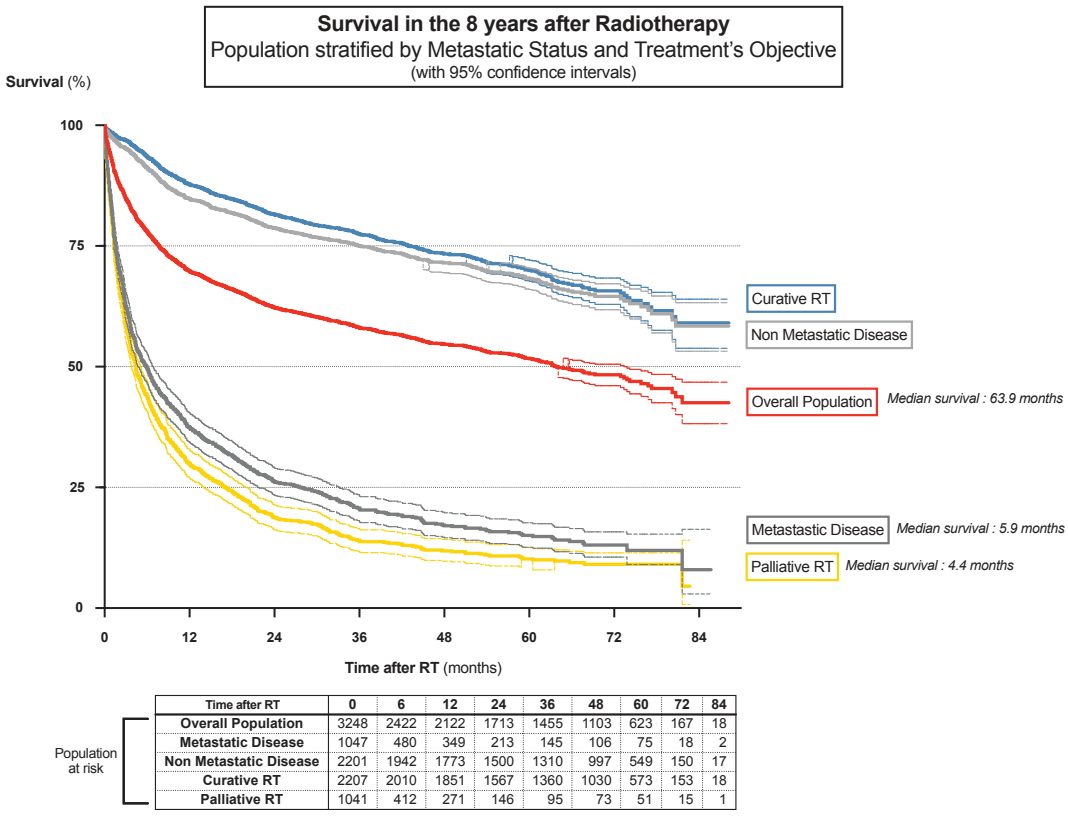


Figure 4: Causes of radiotherapy interruption: population stratified by metastasis disease and treatment's objective

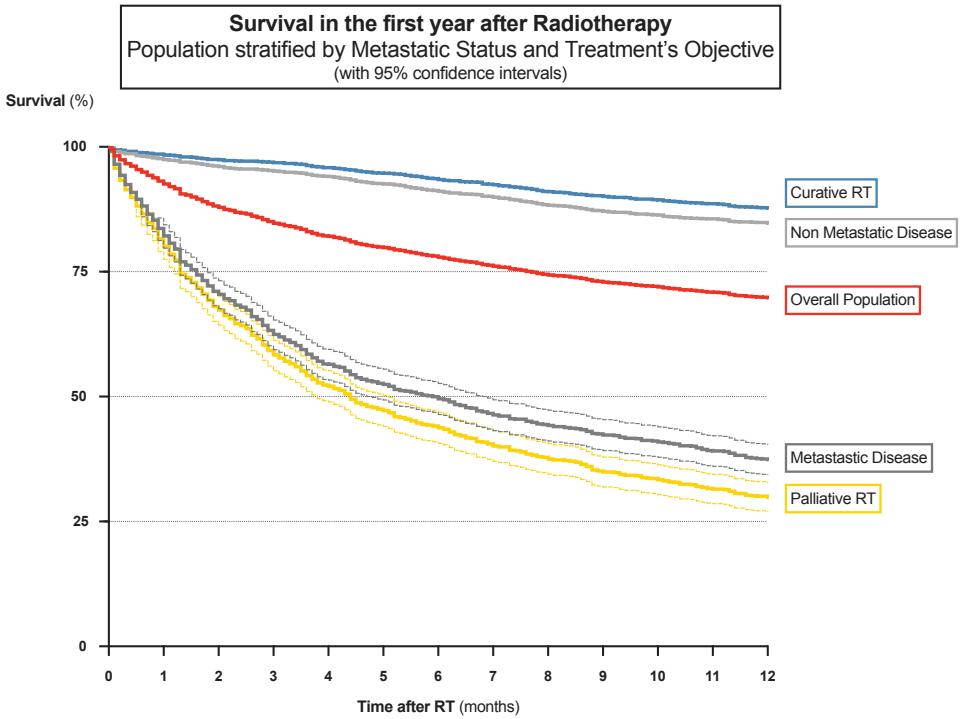
Overall survival

Kaplan Meier curves describing the overall survival of the study population are displayed in Figure 5. The median survival was 63.9 months after RT for the whole population, but it was less than six months for MD patients (5.9 months) and PRT patients (4.4 months), whereas it was not even reached for NMD and CRT patients during the eight-years-follow-up. Log-rank tests showed that survival curves did not differ between those NMD and CRT patients ($p = 0.11$). However, every other pairing was significantly different, with p values < 0.001.

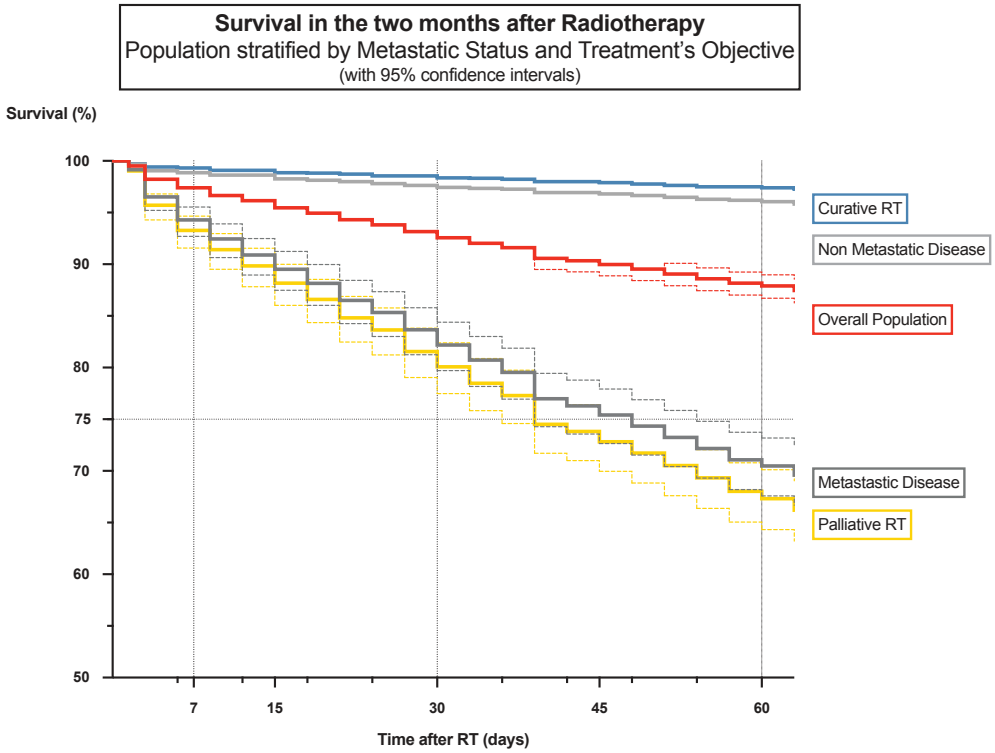
Figure 5: Survival after radiotherapy: Kaplan-Meier curves for overall population, stratified by metastatic status and treatment's objective



Population at risk — Time after RT	0	6	12	24	36	48	60	72	84
Overall Population	3248	2422	2122	1713	1455	1103	623	167	18
Metastatic Disease	1047	480	349	213	145	106	75	18	2
Non Metastatic Disease	2201	1942	1773	1500	1310	997	549	150	17
Curative RT	2207	2010	1851	1567	1360	1030	573	153	18
Palliative RT	1041	412	271	146	95	73	51	15	1



Population at risk — Time after RT	0	0.5	1	2	3	4	5	6	12
Overall Population	3248	3090	2983	2803	2688	2567	2490	2422	2122
Metastatic Disease	1047	933	854	721	634	552	511	480	349
Non Metastatic Disease	2201	2157	2129	2082	2054	2015	1979	1942	1773
Curative RT	2207	2176	2159	2124	2106	2068	2040	2010	1851
Palliative RT	1041	914	824	679	582	499	450	412	271



Population at risk

Time after RT (days)	0	7	15	21	30	39	45	54	60
Overall	3248	3164	3090	3048	2983	2927	2882	2835	2803
Metastatic Disease	1047	988	933	903	854	810	776	743	721
Non Metastatic Disease	2201	2176	2157	2145	2129	2117	2106	2092	2082
Curative RT	2207	2192	2176	2169	2159	2149	2141	2130	2124
Palliative RT	1041	972	914	879	824	778	741	705	679

Deaths in the first year following RT

Characteristics of patients deceased in the 7 days, 30 days, 60 days, 6 months and one year after radiotherapy were gathered in Table 2 and Table 3.

Overall, in the first 7 days after RT, 2.6% of patients died. A month after treatment, this proportion reached 7.2%, then 11.7% after two months. Six months later, one patient out of five was deceased (21.5%) and after one year, approximately one out of three (29.2%). As displayed in Figure 6, the distribution of those deaths was not linear, especially for early observations: the median time of death in the first 30 days after RT was 11.5 days, i.e. more patients died in the first half of the month. This finding is coherent with the slope of the survival curve.

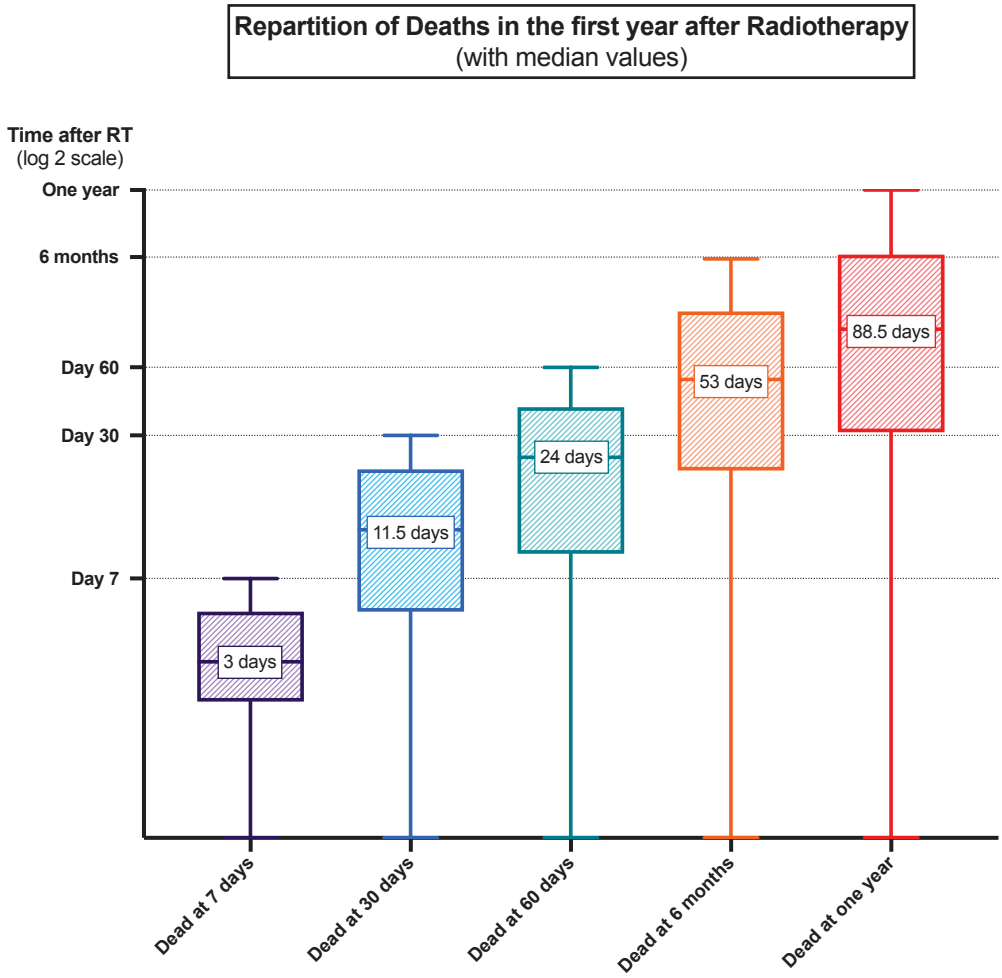


Figure 6: Repartition of deaths in the first year after radiotherapy

Those results were obviously heavily influenced by the metastatic status and the therapeutic objective. MD patients represented 65.7% to 78.2% of deaths, and PRT patients 72.3% to 85.6%. Only 11.9% of the CRT patients where deceased at one year after RT, when 31.3% of PRT patients were already dead at two months. Regarding MD-PRT patients, 6.2% were deceased 7 days after RT, 19.1% after one month and 31.6% at two months. (Figure 7).

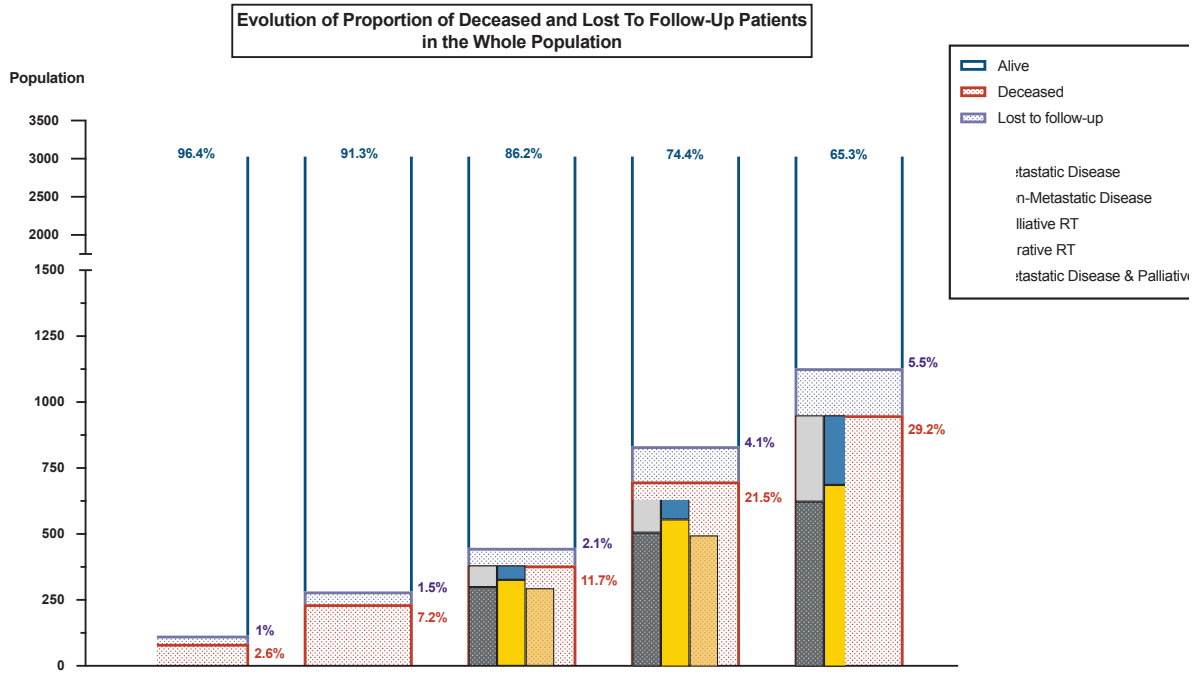


Figure 7: Patients deceased in the 7 days, 30 days, 60 days, 6 months and one year after radiotherapy, stratified by Metastatic Disease and Treatment's Objective

Early deaths (within 60 days) after RT

Most patients deceased in first 60 days were men (57%), with a mean age of 64.7 years old. A majority (32.8%) was ECOG-PS = 3 at the beginning of RT. Almost one out of two was hospitalized when referred to the radiation oncologist (45.4%) and was treated with palliative chemotherapy (49.3%). Amongst them, 40.2% had already been treated with RT at least once. The average treatment of those patients was mostly consistent with palliative protocols: a mean dose of 29.9 Gy in 9.9 fractions during 12.8 days, with a mean dose per fraction of 4.5 Gy. The most frequent primary type was lung cancer (33.3%) followed by digestive organs (18.1%). In this population, breast cancer represented 8.9% of primary cancer site.

Regarding cancer extension, 78% of patients deceased at 60 days presented a metastatic disease, most of them in more than one site, especially in bones (49.1%), brain (36.5%), liver (26.5%) and lung (26.2%), as it was the case in the whole PRT population. Treated site also followed

that pattern: it was more often the brain (33.3%) for metastases control (30.7% of treatments), then it was the rachis (21.8%).

Focusing on patients deceased even earlier (before 30 and 7 days post RT), predominant clinical characteristics remain the same. Nevertheless, we may mention a few interesting nuances: in this group with very short OS, proportion of ECOG-PS = 3 was more important than for the global population of patients deceased at 60 months (46.4% instead of 32.8%) and more people were hospitalized when referred to RT (56% instead of 45.4%).

They were also less amongst patients deceased at 7 days to present a metastatic disease (70.2% instead of 78.2%). Those 25 non-metastatic patients corresponded to an quite older population (mean age of 67.7 years old (p=0.24)) with bad prognosis diseases, more than half of them (15 patients, 60%) being treated for a head-and-neck or an esophagus primary tumor and 3 others (12%) for glioblastoma. Also the majority of them (20 patients, 80%) had interrupted RT treatment because of death unrelated to cancer (44%).

Prognostic factors for the MD-PRT group

Survival analysis of the whole MD-PRT group is displayed in Table 4 and Figure 8A.

Regarding overall survival, significant risk factors were a higher ECOG-PS (HR = 1.70 IC95%(1.57-1.84)), symptomatic brain metastases (HR = 1.39 (1.14-1.68)), primary tumor in lung (HR = 1.22 (1.00-1.49)), larynx (HR = 2.77 (1.12-6.87)) or esophagus (HR = 2.07 (1.13-3.78)), a higher number of metastatic sites (HR = 1.11 (1.04-1.20)) and the presence of bone metastases (HR = 1.25 (1.04-1.51)). Identified protector factors were breast primary (HR = 0.62 (0.50-0.80)), prostate primary (HR = 0.63 (0.42-0.91)), treatment of brain metastases with stereotactic radiotherapy (HR = 0.77 (0.61-0.96)) and treatment of a pelvic localization (HR = 0.67 (0.50-0.90)).

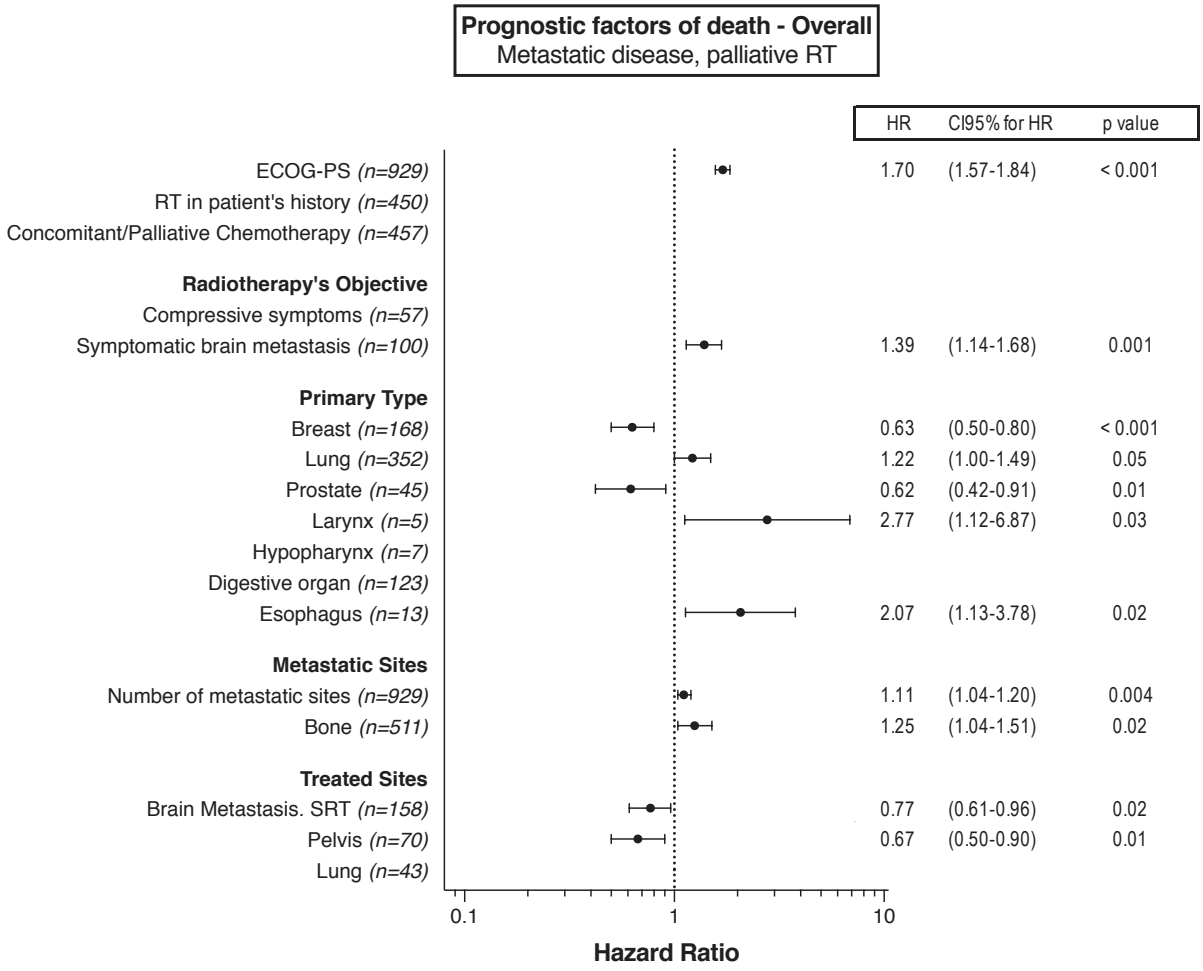


Figure 8: Metastatic disease, palliative RT – Prognostic factor of death
8A: Prognostic factors of death, overall

Prognostic factors for early deaths in the MD-PRT group

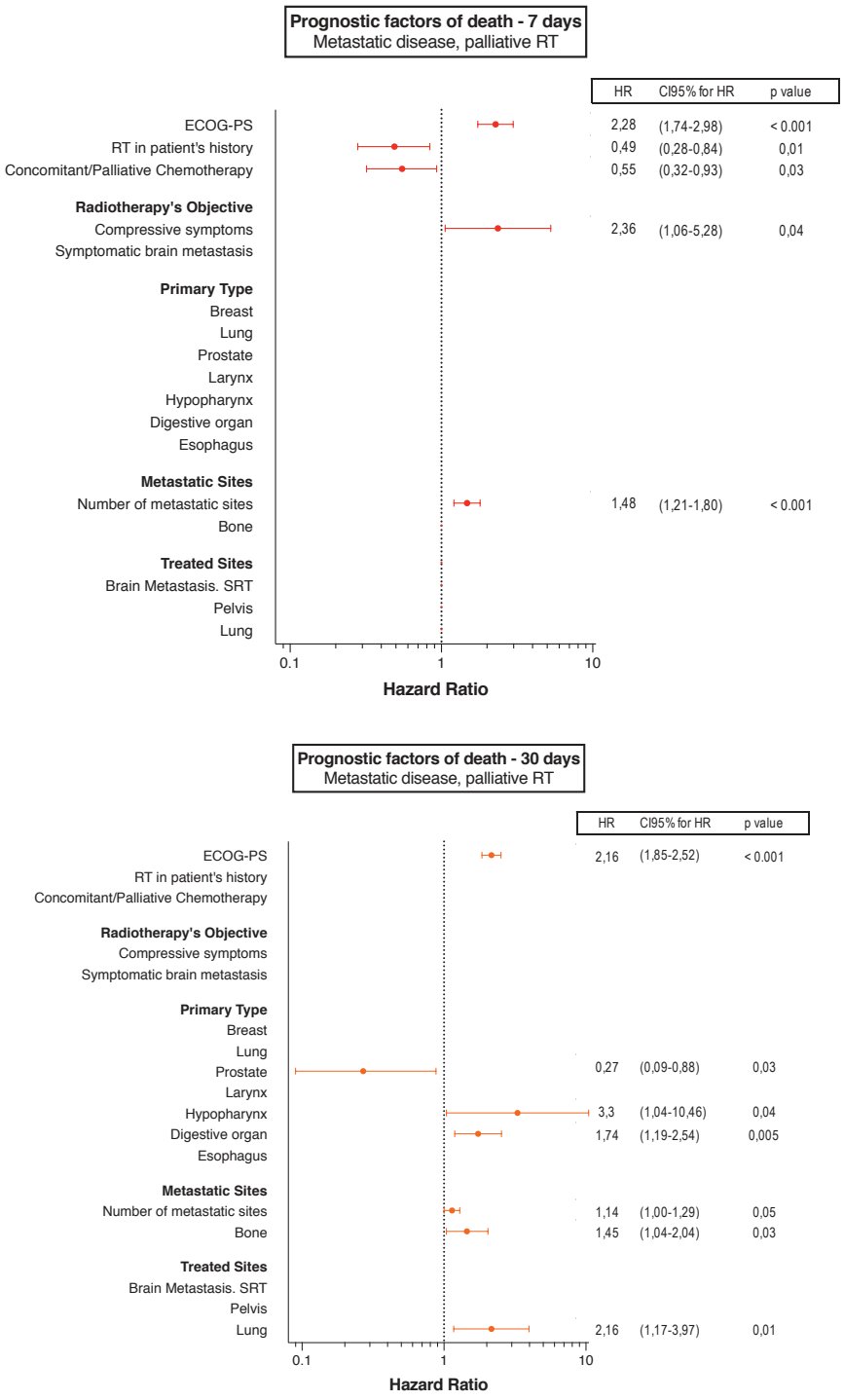
Results of the survival analysis focusing on patients deceased at 7, 30 or 60 days after RT are summed up in Table 5 and Figure 8B.

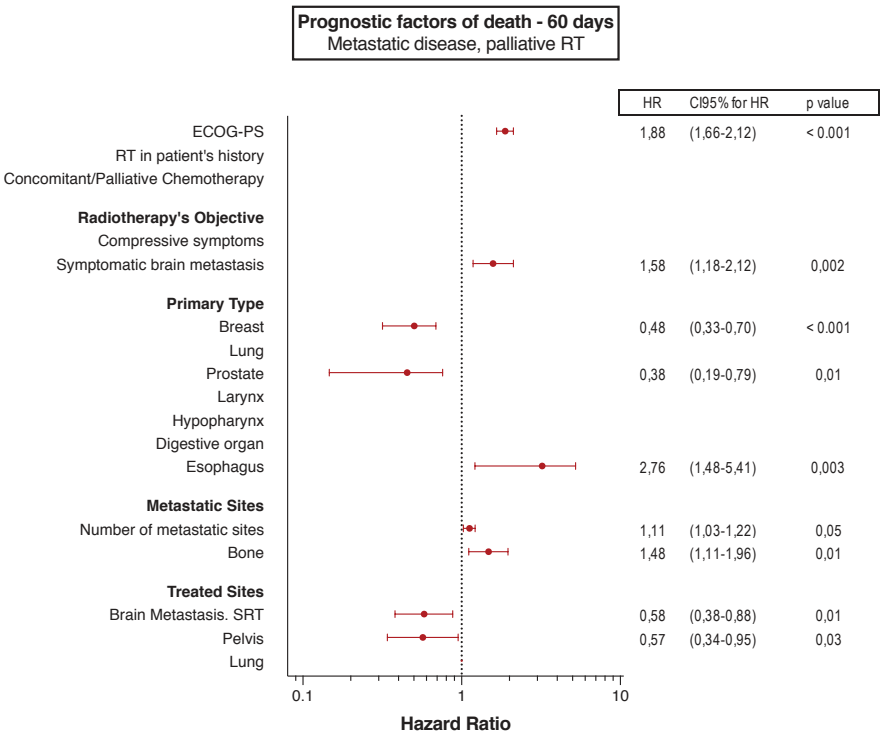
For every of these three subgroups of MD-PRT patients, a higher ECOG-PS (HR from 2.28 to 1.88) and a higher number of metastases (HR from 1.48 to 1.11) were significant risk factors impacting survival, as they were for the global MD-PRT population.

For patients deceased in the first 7 days, the other risk factor was treatment for compressive symptoms (HR = 2.36 (1.06-5.28)). Protective factors were a history of precedent RT treatment (HR = 0.49 (0.28-0.84)) and an ongoing chemotherapy (HR = 0.55 (0.32-0.93)).

For patients deceased at 30 days, other risk factors were a digestive primary (HR = 1.74 (1.19 -2.54), a hypopharynx primary (HR = 3.30 (1.04-10.46)), the presence of bone metastases (HR = 1.45 (1.04-2.04)) and treatment of a lung localization (HR = 2.16 (1.17-3.97)). Prostate primary was a protective factor (HR = 0.27 (0.09-0.88)).

Figure 8B: Prognostic factors of death within 7, 30, 60 days after RT





For patients deceased at 60 days, bone metastases also were a significant risk factor (HR = 1.48 (1.11-1.96)), as were an esophagus primary (HR = 2.76 (1.48-5.41)) and symptomatic brain metastases (HR = 1.58 (1.18-2.12)). Protective factors were primary sites in breast (HR = 0.48 (0.33-0.70)) and prostate (HR = 0.38 (0.19-0.79)), a treatment of pelvic localization (HR = 0.57 (0.34-0.95) and treatment of BM with stereotactic radiotherapy (HR = 0.58 (0.38-0.88).

Survival curves for prognostic factors' evaluation

Kaplan-Meier survival curves exploring those significant prognostic factors are displayed in Figure 9 with results of log-rank tests with adjusted p value.

The log-rank test showed no significant difference in survival between ECOG-PS 0 and 1 (adjusted p value = 0.12), between PS 3 and 4 (p = 0.12), between PS 2 and the overall population (p = 0.47) or between PS 3 and the overall population (p = 0.14). All other pairings were statistically significant (p = 0.015). We then may mention three interesting gaps in survival: the outcome of the overall MD-PRT population was significantly worse than the one

of PS 0 or 1 patients, but significantly better than the one of PS 4 patients, and survival was better for PS 0-1 than for PS 2 patients.

There was no significant variation of survival according to the number of metastases sites. However, the number but survival was significantly better in the presence of only 1 metastatic site compared to 3, 4, 5 or 6 (all p values ≤ 0.035). Two metastatic sites were also correlated to a better outcome when compared to 5 sites, and 5 sites were associated to a worse OS than the overall MD-PRT patients ($p = 0.05$), probably because of the small population presenting with 5 metastatic sites (20 patients, 2.2% of the MD-PRT group).

As for the nature of metastases, bone localizations were the only ones to stand out as a prognostic factor, but survival of patients with bones metastases was not significantly different than the survival of the overall MD-PRT population ($p = 0.06$).

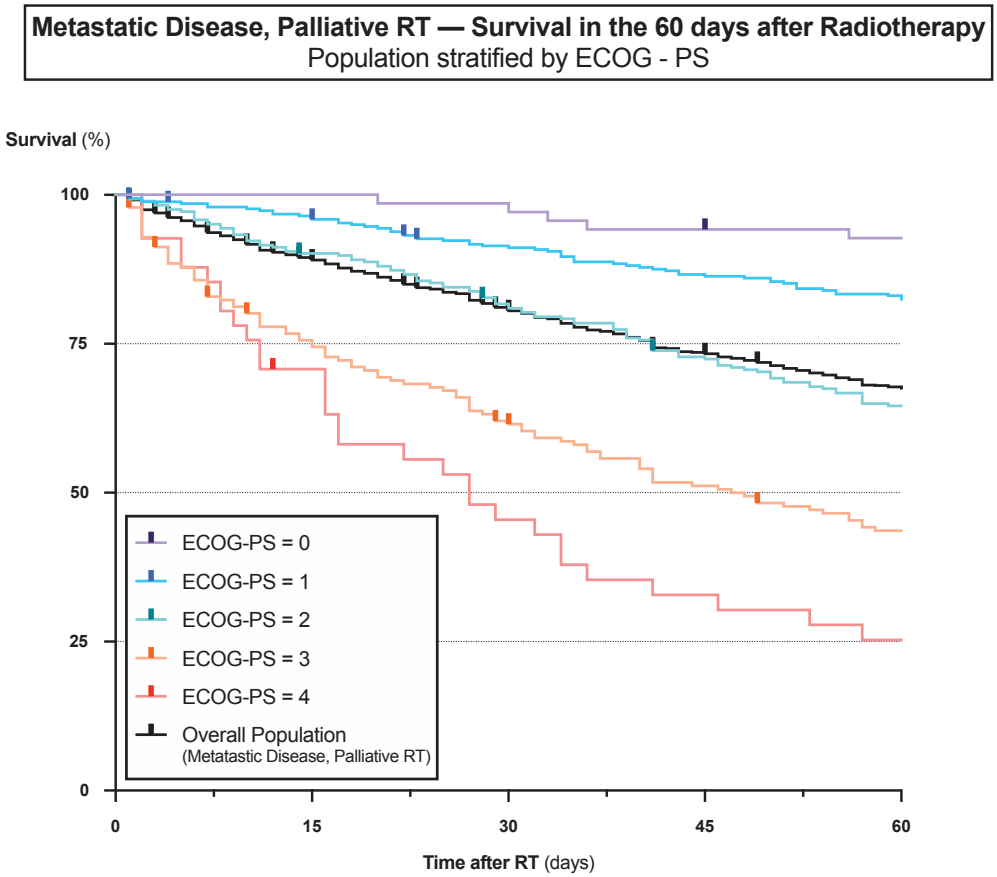
When analyzing primary types, there was no statistical difference in survival between breast and prostate cancer ($p = 0.97$); however, both of them were associated to a better outcome than digestive primaries and the overall MD-PRT population (both $p = 0.006$). Digestive primaries were correlated to significantly worse survival ($p = 0.006$).

As for treated sites, the only significative difference came from patients treated with SRT for brain metastases, whose survival was better than the one of the overall MD-PRT group and of patients treated for lung localization (all p values = 0.001). Interestingly, survival was also better for the SRT group when compared to the outcome of patients referred for symptomatic brain metastases ($p = 0.01$).

Finally, given that patients deceased in first 7 days presented three specific prognostic factors (history of RT treatment, palliative chemotherapy and patient referred for compressive symptoms) that did not stand out in the rest of the MD-PRT population, we chose to test these factors together. When compared between them and to the whole MD-PRT group, none of them was significantly associated to a different outcome in survival. (Figure 10)

Figure 9: Metastatic disease, palliative RT —Variation of survival depending on identified risk factors: Kaplan-Meier curves, log-rank tests and adjusted p values (Holm- Šídák test)

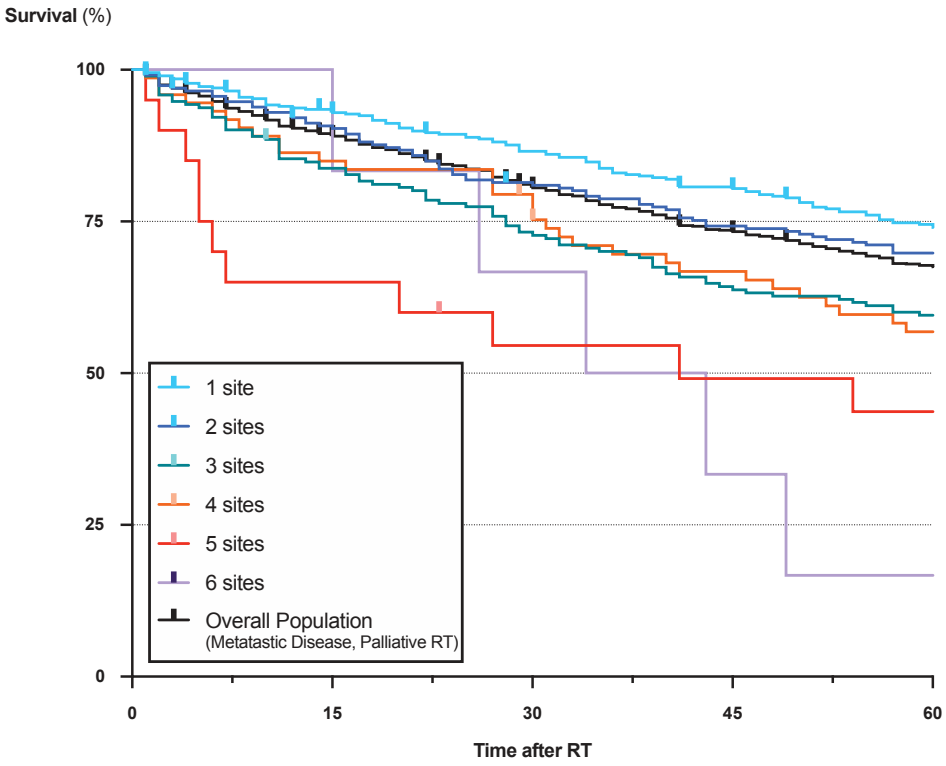
9A: Population stratified by ECOG – PS



Survival curve 1	Survival curve 2	p value (logrank test)	Adjusted p value (Holm-Šídák test)	Significant?
ECOG-PS				
ECOG-PS = 0	ECOG-PS = 1	0,04	0,115	No
	ECOG-PS = 2	<0,001	0,015	**Yes**
	ECOG-PS = 3	<0,001	0,015	**Yes**
	ECOG-PS = 4	<0,001	0,015	**Yes**
	Overall Population	<0,001	0,015	**Yes**
ECOG-PS = 1	ECOG-PS = 2	<0,001	0,015	**Yes**
	ECOG-PS = 3	<0,001	0,015	**Yes**
	ECOG-PS = 4	<0,001	0,015	**Yes**
	Overall Population	<0,001	0,015	**Yes**
ECOG-PS = 2	ECOG-PS = 3	<0,001	0,015	**Yes**
	ECOG-PS = 4	<0,001	0,015	**Yes**
	Overall Population	0,47	0,47	No
ECOG-PS = 3	ECOG-PS = 4	0,03	0,115	No
	Overall Population	0,07	0,135	No
ECOG-PS = 4	Overall Population	<0,001	0,015	**Yes**

9B: Population stratified by number of metastatic sites

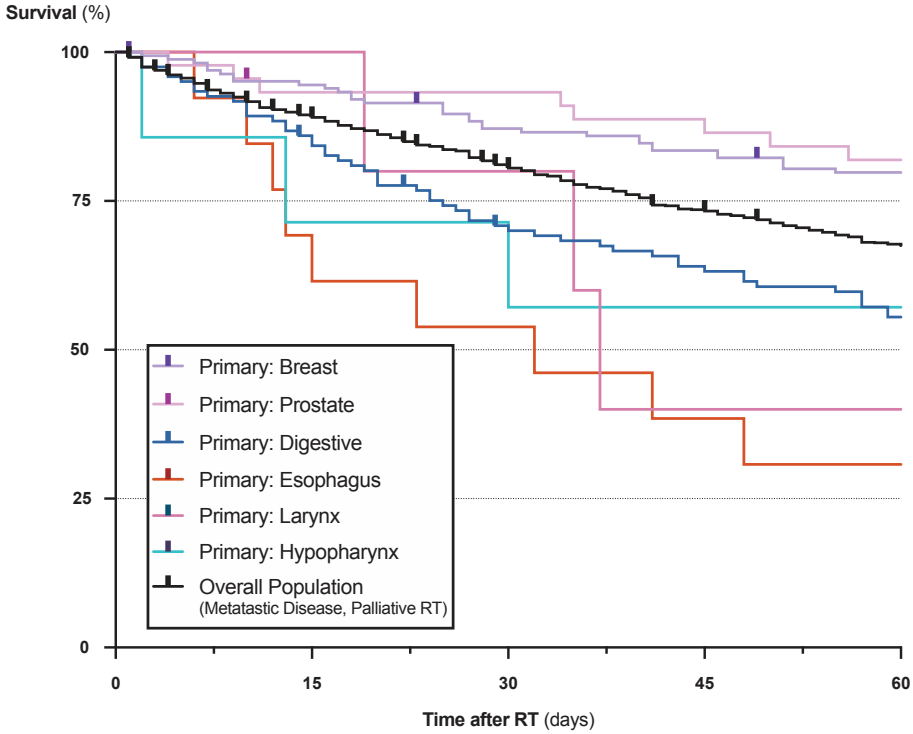
Metastatic Disease, Palliative RT — Survival in the 60 days after Radiotherapy
Population stratified by Number of Metastatic Sites



Survival curve 1	Survival curve 2	p value (logrank test)	Adjusted p value (Holm-Šídák test)	Significant?
Number of Metastatic Sites				
1 site	2 sites	0,2	0,59	No
	3 sites	< 0,001	0,021	**Yes**
	4 sites	0,002	0,035	**Yes**
	5 sites	< 0,001	0,021	**Yes**
	6 sites	< 0,001	0,021	**Yes**
	Overall Population	0,01	0,122	No
2 sites	3 sites	0,02	0,215	No
	4 sites	0,05	0,401	No
	5 sites	0,003	0,05	**Yes (limit)**
	6 sites	0,005	0,072	No
	Overall Population	0,54	0,903	No
3 sites	4 sites	0,84	0,903	No
	5 sites	0,07	0,427	No
	6 sites	0,06	0,427	No
	Overall Population	0,02	0,215	No
4 sites	5 sites	0,13	0,502	No
	6 sites	0,06	0,427	No
	Overall Population	0,07	0,427	No
5 sites	6 sites	0,58	0,903	No
	Overall Population	0,003	0,05	**Yes (limit)**
6 sites	Overall Population	0,006	0,081	No

9C: Population stratified by primary type

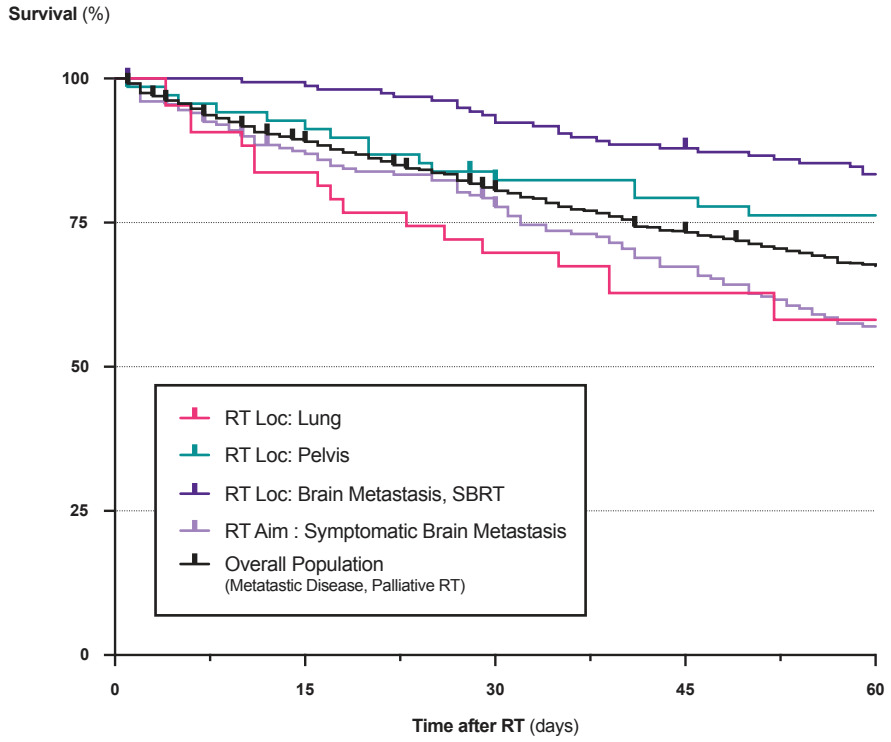
Metastatic Disease, Palliative RT — Survival in the 60 days after Radiotherapy
Population stratified by Primary Type



Survival curve 1	Survival curve 2	p value (logrank test)	Adjusted p value (Holm-Šídák test)	Significant?
Primary Type				
Breast	Primary: Digestive	<0,001	0,021	**Yes**
	Primary: Prostate	0,97	0,970	No
	Primary: Larynx	<0,001	0,021	**Yes**
	Primary: Hypopharynx	<0,001	0,021	**Yes**
	Primary: Esophagus	<0,001	0,021	**Yes**
	Overall Population	<0,001	0,021	**Yes**
Digestive organs	Primary: Prostate	0,001	0,021	**Yes**
	Primary: Larynx	0.07	0,353	No
	Primary: Hypopharynx	0.11	0,442	No
	Primary: Esophagus	<0,001	0,021	**Yes**
	Overall Population	<0,001	0,021	**Yes**
Prostate	Primary: Larynx	<0,001	0,021	**Yes**
	Primary: Hypopharynx	<0,001	0,021	**Yes**
	Primary: Esophagus	<0,001	0,021	**Yes**
	Overall Population	<0,001	0,021	**Yes**
Larynx	Primary: Hypopharynx	0.54	0,903	No
	Primary: Esophagus	0.61	0,903	No
	Overall Population	0.003	0,024	**Yes**
Hypopharynx	Primary: Esophagus	0.15	0,478	No
	Overall Population	0.004	0,028	**Yes**
Esophagus	Overall Population	<0,001	0,021	**Yes**

9D: Population stratified by treated location

Metastatic Disease, Palliative RT — Survival in the 60 days after Radiotherapy
Population stratified by Treated Location



Survival curve 1	Survival curve 2	p value (logrank test)	Adjusted p value (Holm-Šídák test)	Significant?
Treated Site and Radiotherapy's Objective				
Lung	Pelvis	0,04	0,185	No
	Brain Metastasis, SRT	<0,001	0,01	**Yes**
	Symptomatic BM	0,93	0,93	No
	Overall Population	0,15	0,453	No
Pelvis	Brain Metastasis, SRT	0,14	0,453	No
	Symptomatic BM	0,01	0,059	No
	Overall Population	0,17	0,453	No
Brain Metastasis, SRT	Symptomatic BM	<0,001	0,01	**Yes**
	Overall Population	<0,001	0,01	**Yes**
Symptomatic BM	Overall Population	0,008	0,055	No

9E: Comparison between overall population and patients with bones metastasis

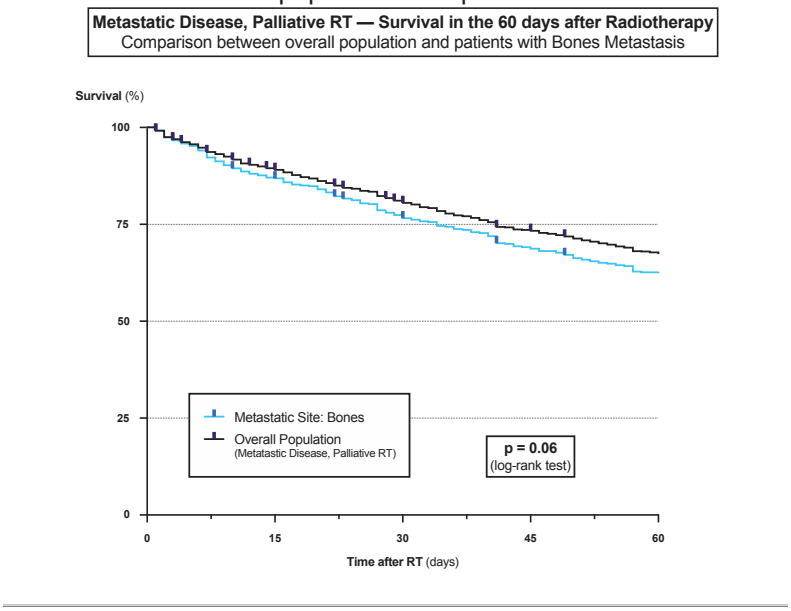
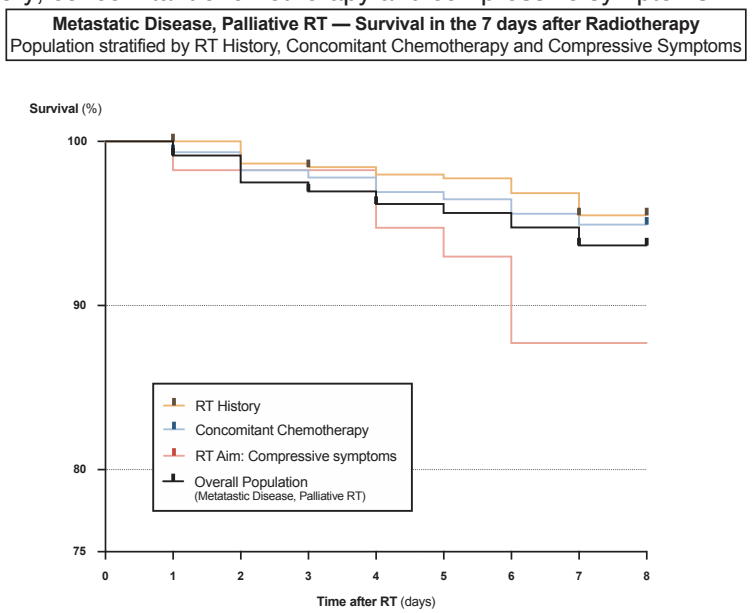


Figure 10: Metastatic disease, palliative RT — survival in the 7 days after radiotherapy : population stratified by RT history, concomitant chemotherapy and compressive symptoms



Survival curve 1	Survival curve 2	p value (logrank test)	Adjusted p value (Holm-Šídák test)	Significant?
Risk factors specific to 7 first days				
RT in patient's history	Compressive symptoms	0,01	0,059	No
	Concomitant Chemotherapy	0,56	0,686	No
	Overall Population	0,16	0,407	No
RT's Objective: Compressive symptoms	Concomitant Chemotherapy	0,04	0,185	No
	Overall Population	0,08	0,284	No
Concomitant Chemotherapy	Overall Population	0,44	0,686	No

All these prognostic factors impacting our cohort's survival are summed up in Table 6, with proposition of prognostic value based upon the aspect of survival curves, the HR value and the clinical relevance of each factor.

Table 6: Patients with Metastatic Disease and treated with Palliative Radiotherapy – Prognostic Factors with an impact on observed survival and proposition of prognostic value based upon aspect of survival curves, HR value, clinical relevance

Prognostic value:
- - : Important protective factor / - : Protective factor / o: None / +: Risk factor / ++ : Important risk factor

ECOG-PS	Observed categories	**0 or 1**	**2**	**3**	**4**	
	Prognostic value	**-**	**o**	**+**	**++**	
	Hazard Ratio (HR)		*Death at 7 days (D7): 2.28 (1.74-2.98)* *Death at 30 days (D30): 2.16 (1.85-2.52)* *Death at 60 days (D60): 1.88 (1.66-2.12)*			
Metastatic Sites	Observed categories	**1 site**	**2 sites**	**3 or 4 sites**	**5 sites or more**	
	Prognostic value	**-**	**o**	**+**	**++**	
			HR D7: 1.48 (1.21-1.80) *HR D30: 1.14 (1.00-1.29)* *HR D60: 1.11 (1.03-1.22)*			
Primary Type	Observed categories	**Breast**	**Prostate**	**Digestive Organs** [a]	**Hypopharynx**	**Esophagus**
	Prognostic value	**-**	**-**	**+**	**++**	**++**
		HR D60: 0.46 (0.33-0.70)	*HR D30: 0.27 (0.09-0.88)* *HR D60: 0.38 (0.19-0.79)*	*HR D30: 1.74 (1.19-2.54)*	*HR D30: 3.30 (1.04-10.46)*	*HR D60: 2.76 (1.48-5.41)*
Treated Site	Observed categories	**Asymptomatic Brain Metastasis treated with SRT** [b]		**Compressive Mediastinal Loc** [c]		
	Prognostic value	**- -**		**+ +**		
		/		/		

[a] : other than esophagus, rectum and anal canal
[b] : this category being construct with the opposition of the good prognostic value of SRT to the bad prognostic value of symptomatic brain metastasis, no HR was calculated
[c] : this category being construct with both bad prognostic values of referring for compressive symptoms and treatment for mediastinal localization, the opposition of the good prognostic value of SRT to the bad prognostic value of symptomatic brain metastasis, no HR was calculated

DISCUSSION

The main goal of this study was to identify prognostic factors of death in the first two months after palliative RT for patients presenting with a metastatic disease. Secondary objectives were the attribution of relative weight to those prognostic factors, and the demographic study of the whole patients' population.

The relevance of this subject was confirmed by the descriptive analysis of patients who did not complete the RT course: a majority were treated with palliative intend and stopped the treatment for medical reasons, most of the time because of cancer progression. This finding is coherent with the already investigated fact that palliative RT toxicities are most of time quite manageable, and that patients stopping symptomatic RT treatment do so because of the disease more than because of the treatment itself.[27] There is therefore an important place for a prognostic evaluation in palliative RT, even though survival is not the treatment's objective.

Demographic data:

One of the main interests of this study, despite being monocentric, was its large population and its long follow-up of more than eight years, allowing the collect of very mature data concerning the first year after treatment. We also had a reasonably low proportion of lost to follow-up in this same first year, because we took in account a quite common bias in studies concerning palliative RT, i.e. that most patients treated only in symptomatic intent are not systematically followed by the radiation oncologist: in order to not overwhelm a limited radiotherapy consultation schedule and to limit potentially harmful transports for already fragile patients, these latter ones are most often referred back to their supervising specialist or general practitioner. Looking for those patients' outcome is important because those are the most

vulnerable ones, especially at risk of dying in the critical period we were analyzing. The avoidance of this bias thus significantly improved the representativity of our study population. The population was also conform to demographic data coming from literature: we did obtain between 30% and 50% of palliative treatments, 25 to 30% of patients treated for breast cancer and 10 to 20% for lung cancer, and the main metastatic site was the bone, followed by the brain.[28–31] Disparities in RT schedules where essentially noted between curative and palliative regimens and were coherent with usual protocols used in each of these categories, i.e. less important doses (8 to 30 Gy) in less fractions (1 to 10) and thus more important doses per fraction (more than 2 Gy). Repartition of causes of palliative treatment were also quite coherent with other studies.[32, 27]

We choose to tolerate a quite detailed stratification of patients, especially regarding primary tumors' and metastases' characteristics, hoping that the important population would compensate for the risk of dilution of the effect and that it would allow the description of some quite subtle variables. We indeed were able to detect some prognostic value for larynx, hypopharynx and esophagus primitives in the early death of MD-PRT patients. Even though those findings must be treated with caution given the very small size of corresponding samples, they still are clinically interesting, because one might argue that they correspond to a same pathological entity (neck cancer) related to same risk factors (tobacco and alcohol intoxication) for the same type of patients with comparable comorbidities. It seems therefore quite possible that those primitives are correlated with a worse outcome, because when those already quite fragile patients reach a metastatic and palliative state, they might be significantly "more ill" than the mean MD-PRT population.

Further limitations of our study included other potential biases due to its retrospective design, especially lacking clinical data of interest. We may mention the absence of delay between cancer diagnostic and analyzed RT course, which was difficult to obtain due to technical issues;

we try to compensate for this by collecting history of precedent treatment by RT, which was correlated to cancer stage and time passed with a metastatic disease. Another missing data was the presence of significant comorbidities, which was deemed to complex to assess upfront (which diseases were most significative, which ones were strongly linked to survival, which ones influenced the treatment choice and at what degree…), with too much data lacking in RT files (especially regarding the severity of those comorbidities) to draw any solid conclusion. To indirectly describe potential comorbidities and vulnerabilities, we preferred to collect the ECOG-PS, a much stronger and well documented parameter.

At last, we did not compile any information regarding symptoms improvement. Firstly, it was not the purpose of this study, which aimed to define futile RT by analyzing early deaths. Secondly, as we discussed it above, the data was often missing (lost to follow-up, not explicit in files) or submitting to variation between patient's and physician's opinion. We therefore choose to stick to a stronger survival analysis. However, some further research in this field might be of interest, given that other studies found that up to 26% of patients deceased in the first month following RT still experienced some symptom improvement.[33]

Survival analysis:

Our findings regarding survival of the global population and the different subgroups were consistent with the literature. We might mention the proportion of deaths in the first 30 days after palliative RT, i.e. patients treated in their last month of life, which in most studies represent 10% to 15% of PRT patients.[33]

When describing the whole population deceased in the first 7 days after RT (84 patients), we mentioned a less important proportion of metastatic diseases than amongst patients deceased at 30 or 60 days. There was not significant variable explaining this finding, but those non-metastatic patients present amongst the very early deceased tended to be older and to die from

non-cancer related causes. They also presented a majority of neck and esophagus tumors, which seemed coherent with our observation of an early prognostic value of those localizations.

Prognostic factors: statistical analysis:

Despite describing demographic data for the whole population, we chose to focus only on MD-PRT patients when looking for prognostic factors of death at 60 days. We already explained why we analyzed early survival only for palliative patients. Removing the non-metastatic palliative patients was not a statistical choice, given that survival of both MD-PRT and NMD-PRT groups were not significantly different (log-rank test, $p = 0.08$). We excluded NMD-PRT patients because they corresponded to a clinically different population, more frequently recused for curative treatment because of older age or severe comorbidities, which could have biased the search for cancer related prognostic factors.

When choosing between variables correlated to each other in early death analysis, we discarded the presence of lung or liver metastases as variables to the profit of the number of metastatic sites, which was a more constant variable from one time period (7 days, 30 days, 60 days) to another. It also seemed clinically more relevant, because we didn't dispose of the number of metastases in lung or liver for the same patient and it seemed dubious to give the same prognostic value to one or more than ten localizations in one same organ.

Regarding rachis treatment, we preferred the variable taking in account the presence of symptomatic epiduritis because it was more precise and because it was a localization known for having a worse prognostic than a painful bone metastasis in a vertebra. Following the same reasoning, we discarded the hospitalization criteria to the benefit of the ECOG-PS, a stronger and more acute representation of patient's global status.

At last, choices between different modalities of treatment for brain metastases were essentially guided by uniformization of variables to facilitate comparison between time periods.

Prognostic factors: results for overall survival

Regarding overall survival of MD-PRT patients, most of significant prognostic factors detected in this study were coherent with findings of the literature, most notably a higher ECOG-PS (risk factor)[33], lung primary (risk factor), breast and prostate primaries (protective factor) and bone metastases (risk factor).

The increase of number of metastatic sites worsening prognosis was also expected; we should emphasize the clear gap in survival between patients presenting a unique metastatic site and the rest of MD-PRT population, even though there wasn't any oligometastatic patient in the analysis (they were in the MD-CRT group).

Concerning brain metastasis, their presence wasn't a prognosis factor in itself, but it was most certainly because of intrinsic heterogeneity in the population, asymptomatic brain metastases and SRT treatment being protective factors whereas symptomatic brain metastases and WBRT were risk factors.

Otherwise, we noticed again the fragility of MD-PRT patients presenting with larynx and esophagus primaries (risk factors), but pelvic RT as a protective factor was more surprising; those treatments were in fact patients with bone metastases referred for pain control (14 out of 16 patients), which might correspond to a less menacing disease than other ones treated with palliative RT, but there was no clear explanation regarding why a symptomatic bone metastasis would be of better prognosis if located in pelvic bones.

At last, patients' age was significative only in univariate analysis, and even then, was correlated to an hazard ratio of 1, so without any positive or negative prognostic value. There is a lack of specific research data on the subject, but a few retrospective studies [34, 35] showed that there was no significant reason to withdraw palliative RT after 75 or 80 years old, which seems coherent with our findings.

Prognostic factors: results for early deaths

Regarding prognostic factors of a very early death, within the first 7 days after RT, the only risk factor related to the cancer itself was the referral for compressive symptoms, an easily understandable worse outcome given that it concerned only 7 patients all presenting an obstructive localization in throat (2 patients) or mediastinum (5 patients). Otherwise, a precedent RT treatment and ongoing systemic treatments were protective factors, certainly because they are correlated with less aggressive metastatic diseases (if the patient survives longer with metastases, the probability of multiple, successive RT treatments increases) and better global status (a clinically deeply altered patient will not be treated with chemotherapy).

Prognostic factors of death in the first 30 days also included palliative RT on mediastinum as a risk factor; even though it was significant only through the "treated site: lung and mediastinum" variable, it appeared that 10 out of 13 concerned patients were referred for compressive symptoms. Hypopharynx primary was a risk factor certainly for the same reasons than esophagus (death at 60 days) and larynx (overall survival) cancers. At last, the worse prognosis of digestive primaries (esophagus and rectum excluded, i.e. mostly stomach and colon cancer) may seem surprising, but there are data in literature backing up the fact that those cancers are associated with a worst outcome when they evolve into a metastatic and palliative stage, most notably when they present brain metastases.[3]

As for prognostic factors of death at 60 days, they roughly correspond to those described for overall survival.

Prognostic score:

Construction of a relevant prognostic score was an intricate question. We manage to give some weight to factors with a comparison between their correlated survivals, but as we saw above, at lot of significant variables overlapped inside or between time periods, with hazard ratios being

not constant over time. There is therefore a need for further analysis and a quite complex statistical input to give the observed prognostic factors their adequate value.

So we stuck to a simple but easy to use score based upon qualitative ranking (important protective factor, protective factor, no prognostic value, risk factor, important risk factor) without any quantitative classification. This allowed us to take in account some of the most subtle associations that we found, as asymptomatic brain metastases and SRT, or compressive mediastinum localizations, without prejudging their true statistical value.

Some other studies proposed simple technics to construct a quantitative score, for example based upon HR values[36], or composed with arbitrary numerical coefficients. However, when discussing futile palliative RT, it seemed not relevant to propose a quantitative score at any cost. First of all, it would have implied to sacrifice some of the small variations that we observed, when these subtilities were exactly what we were looking for when trying to estimate survival at a daily scale: getting rid of them for the sake of an artificial scoring seemed counter-productive. Secondly, we had to keep in mind that we were dealing with a quite sensitive and complex situation, i.e. limitation of therapeutics near the end of life. As every other treatment in palliative care, for the clinician symptomatic RT is not a binary question of "can we or can we not?", it's more of a "should we or should we not?" way of thinking. We discussing symptom improvement and quality of life, even the most precise prognostic score should be put in balance with clinical judgement and communication with the patient; a half-assessed tool would simply be of no use.

However, there really is a place for prognostic scores in palliative care. As we saw, despite the expected delay of 4 to 6 weeks before full clinical effect, in the MD-PRT population one patient out of five was dead in the month following palliative RT, and that proportion reached almost one out of three at two months. All those patients were exposed to a futile RT. As alarming as these important proportions are, they are not surprising: other studies proved that physicians do

not perform well when trying to predict the outcome of patients with extensive cancer,[37–39] they clearly tend to overestimate survival [40, 41] and therefore to prescribe futile treatments. Moreover, patients themselves struggle to estimate not only their own survival[42], but also the quality of life that they deemed important and the kind of treatment they are ready to endure. So to mirror our precedent argument regarding the value of clinical judgement and communication in palliative context, they are clearly not enough: there is a mighty need of strong, objective data to sustain the final decision to treat or not.

Finally, we may mention another important application of objective prognostic scores in palliative care: a significant amount of those patients are not able to decide for themselves anymore. Of course, the most obvious of these situations are cognitive impairment caused by brain tumors, brain metastasis or neurological symptoms related to a systemic complication of cancer (electrolytic imbalance, paraneoplastic syndrome…). Yet there are also more subtle cases, where the physical pain or the psychological distress of a confrontation with the end of life may severely cripple the patients' autonomy. Those complex cases imply most of the time the patient's healthcare proxy and their family, who are then supposed to bear a part of the responsibility of treatment decision. It seems essential for the physician to be able to present them with objective data which would guide the common decision, especially if this choice involves some limitation of care which can be quite guilt inducing and traumatic for patient's loved ones.

CONCLUSION

In a representative population of cancer patients treated by radiotherapy, potentially futile RT concerned as much a one palliative treatment out of three. For patients presenting with a metastatic disease and referred for symptomatic RT, risk factors of death in the two following months were an ECOG-PS 3 or 4, invasion of more than two metastatic sites, cancer primary in the pharyngo-larynx or the digestive system (rectum and anal canal excepted) and a compressive mediastinal localization. Protective factors were an ECOG-PS 0 or 1, invasion of a unique metastatic site, cancer primary in the breast or the prostate and asymptomatic brain metastases accessible to stereotactic RT. Further investigation and statistical analysis are needed to determine the exact weight of those factors, which could help the physician to decide, after concerting with the patient and their family, if radiotherapy really is the more adapted option or if its predictable futility may guide towards a less invasive type of symptomatic treatment.

REFERENCES

1. Kasman DL: When is medical treatment futile? A guide for students, residents, and physicians. J Gen Intern Med 19:1053–1056, 2004
2. Samant R, Tucker T: How should we describe the benefits of palliative radiotherapy? Curr Oncol 13:230–234, 2006
3. Taillibert S, Le Rhun É: Épidémiologie des lésions métastatiques cérébrales. Cancer/Radiothérapie 19:3–9, 2015
4. Roila F, Cortesi E: Quality of life as a primary end point in oncology. Annals of Oncology 12:S3–S6, 2001
5. Langendijk JA, ten Velde GPM, Aaronson NK, et al: Quality of life after palliative radiotherapy in non-small cell lung cancer: a prospective study. International Journal of Radiation Oncology*Biology*Physics 47:149–155, 2000
6. Tong D, Gillick L, Hendrickson FR: The palliation of symptomatic osseous metastases final results of the study by the radiation therapy oncology group. Cancer 50:893–899, 1982
7. Spencer K, Morris E, Dugdale E, et al: 30 day mortality in adult palliative radiotherapy – A retrospective population based study of 14,972 treatment episodes. Radiotherapy and Oncology 115:264–271, 2015
8. Hird A, Chow E, Zhang L, et al: Determining the Incidence of Pain Flare Following Palliative Radiotherapy for Symptomatic Bone Metastases: Results From Three Canadian Cancer Centers. International Journal of Radiation Oncology*Biology*Physics 75:193–197, 2009
9. Mulvenna P, Nankivell M, Barton R, et al: Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. The Lancet 388:2004–2014, 2016
10. Haaser T: Prise en charge des patients en fin de vie en service de radiothérapie [Internet], in Fins de vie, éthique et société. Toulouse, ERES, 2016, pp 281–285Available from: https://www.cairn.info/fins-de-vie-ethique-et-societe--9782749251905-p-281.htm
11. Bradburn MJ, Clark TG, Love SB, et al: Survival analysis part II: multivariate data analysis--an introduction to concepts and methods. Br J Cancer 89:431–436, 2003
12. Bradburn MJ, Clark TG, Love SB, et al: Survival analysis Part III: multivariate data analysis -- choosing a model and assessing its adequacy and fit. Br J Cancer 89:605–611, 2003
13. Cox DR: Regression Models and Life-Tables. Journal of the Royal Statistical Society Series B (Methodological) 34:187–220, 1972
14. Farrar DE, Glauber RR: Multicollinearity in Regression Analysis: The Problem Revisited. The Review of Economics and Statistics 49:92–107, 1967
15. Šidák Z: Rectangular Confidence Regions for the Means of Multivariate Normal Distributions. Journal of the American Statistical Association 62:626–633, 1967
16. R Core Team (2019): R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Version 3.5.0 [Internet]. 2019Available from: https://www.R-project.org/
17. Kazuki Yoshida (2019).: tableone: Create “Table 1” to Describe Baseline Characteristics. R package version 0.10.0. [Internet]Available from: https://CRAN.R-project.org/package=tableone
18. Therneau T (2015): survival : A Package for Survival Analysis in S. R package version 2.38. [Internet]Available from: https://CRAN.R-project.org/package=survival
19. Alboukadel Kassambara and Marcin Kosinski (2019): survminer: Drawing Survival

Curves using “ggplot2”. R package version 0.4.4. [Internet]Available from: https://CRAN.R-project.org/package=survminer
20. Barret Schloerke, Jason Crowley, Di Cook, Francois Briatte, Moritz Marbach, Edwin Thoen, Amos Elberg and Joseph Larmarange: GGally: Extension to “ggplot2”. R package version 1.4.0. [Internet]. 2018Available from: https://CRAN.R-project.org/package=GGally
21. Imdadullah, M. A M: mctest: An R Package for Deteection of Collinearity among Regressors. R package version 1.2. [Internet]. 2018Available from: https://CRAN.R-project.org/package=mctest
22. Taiyun Wei and Viliam Simko: R package “corrplot”: Visualization of a Correlation Matrix (Version 0.84). [Internet]. 2017Available from: https://github.com/taiyun/corrplot
23. Wickham, H.: ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York, 2016
24. International-Harvard Statistical Consulting Company: My.stepwise: Stepwise Variable Selection Procedures for Regression Analysis. R package version 0.1.0. [Internet]. 2017Available from: https://CRAN.R-project.org/package=My.stepwise
25. GraphPad Prism for MacOS [Internet]. La Jolla California USA, GraphPad SoftwareAvailable from: https://www.graphpad.com
26. Motulsky, H. J.: GraphPad Statistics Guide [Internet], 2019Available from: http://www.graphpad.com/guides/prism/7/statistics/index.htm
27. Clément-Zhao A, Luu M, Bibault J-E, et al: Effective delivery of palliative radiotherapy: A prospective study. Cancer/Radiothérapie 23:365–369, 2019
28. Ferlay J, Soerjomataram I, Dikshit R, et al: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer 136:E359–E386, 2015
29. Van Oorschot B, Schuler M, Simon A, et al: Patterns of Care and Course of Symptoms in Palliative Radiotherapy. Strahlentherapie und Onkologie 187:461, 2011
30. Nombre de patients traités par radiothérapie en fonction de la localisation [Internet], 2019Available from: http://lesdonnees.e-cancer.fr/Themes/Soins/La-radiotherapie/L-activite-et-les-techniques-de-traitement/La-radiotherapie-externe2/Nombre-de-patients-traites-par-radiotherapie-en-fonction-de-la-localisation#graphique
31. Les cancers en France en 2018 - L’essentiel des faits et chiffres (édition 2019) [Internet], 2019Available from: https://www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/Les-cancers-en-France-en-2018-L-essentiel-des-faits-et-chiffres-edition-2019
32. Angelo K, Norum J, Dalhaug A, et al: Development and Validation of a Model Predicting Short Survival (Death Within 30 Days) After Palliative Radiotherapy. Anticancer Research 34:877–885, 2014
33. Park KR, Lee CG, Tseng YD, et al: Palliative radiation therapy in the last 30 days of life: A systematic review. Radiotherapy and Oncology 125:193–199, 2017
34. Campos S, Presutti R, Zhang L, et al: Elderly Patients With Painful Bone Metastases Should be Offered Palliative Radiotherapy. International Journal of Radiation Oncology*Biology*Physics 76:1500–1506, 2010
35. Nieder C, Angelo K, Haukland E, et al: Survival After Palliative Radiotherapy in Geriatric Cancer Patients. Anticancer Research 34:6641–6645, 2014
36. Nieder C, Angelo K, Dalhaug A, et al: Palliative radiotherapy during the last month of life: Predictability for referring physicians and radiation oncologists. Letters 10:3043–3049, 2015
37. Bruera E, Miller MJ, Kuehn N, et al: Estimate of survival of patients admitted to a Palliative Care Unit: A prospective study. Journal of Pain and Symptom Management 7:82–86, 1992
38. Glare P, Virik K, Jones M, et al: A systematic review of physicians’ survival predictions

in terminally ill cancer patients. BMJ 327:195, 2003
39. Tseng YD, Krishnan MS, Sullivan AJ, et al: How Radiation Oncologists Evaluate and Incorporate Life Expectancy Estimates Into the Treatment of Palliative Cancer Patients: A Survey-Based Study. International Journal of Radiation Oncology*Biology*Physics 87:471–478, 2013
40. Kondziolka D, Parry, P. V., L. Dade Lunsford, et al: The accuracy of predicting survival in individual patients with cancer. Journal of Neurosurgery JNS 120:24–30, 2014
41. Barnes EA, Chow E, Tsao MN, et al: Physician Expectations of Treatment Outcomes for Patients With Brain Metastases Referred for Whole Brain Radiotherapy. International Journal of Radiation Oncology • Biology • Physics 76:187–192, 2010
42. Edwards M, Davies M, Edwards A: What are the external influences on information exchange and shared decision-making in healthcare consultations: A meta-synthesis of the literature. Patient Education and Counseling 75:37–52, 2009

TABLES

Table 1A: **Characteristics of patients' population**, stratified by Metastatic Status and Therapeutic Objective (Curative or Palliative Radiotherapy)

	Overall Population	Metastatic Status		Therapeutic Objective	
		Non-Metastatic Disease	Metastatic Disease	Curative Radiotherapy	Palliative Radiotherapy
n (%)	3248	2201 (67.8%)	1047 (32.2%)	2207 (67.9%)	1041 (32.1%)
Median follow-up (range, months)	28,0 (0 – 88.2)	42,6 (0 – 88.2)	4,50 (0 – 85.7)	44,3 (0 – 88.2)	3,60 (0 – 82.7)
Therapeutic Objective					
Curative Radiotherapy	2207	2089 (94.7%)	118 (5.3%)	-	-
Palliative Radiotherapy	1041	112 (10.8%)	929 (89.2%)	-	-
Metastatic Status					
Non-Metastatic Disease	2201	-	-	2089 (94.9%)	112 (5.1%)
Metastatic Disease	1047	-	-	118 (11.3%)	929 (88.7%)
PATIENTS' CHARACTERISTICS					
Sex = Female	1872 (57.6%)	1372 (62.3%)	500 (47.8%)	1381 (62.6%)	491 (47.2%)
Age Mean (s.d.) (extreme values, y.o.)	63.21 (12.71) (19 – 98)	63.26 (13.00) [a] (19 – 95)	63.10 (12.09) [a] (19 – 98)	62.73 (12.78) (19 – 91)	64.21 (12.52) (19 – 98)
ECOG-PS					
0	1089 (33.5%)	976 (44.4%)	113 (10.8%)	1015 (46%)	74 (7.1%)
1	1316 (40.5%)	912 (41.6%)	404 (38.6%)	947 (43%)	369 (35.5%)
2	530 (16.3%)	231 (10.7%)	299 (28.6%)	208 (9.4%)	322 (30.9%)
3	258 (7.9%)	69 (3.2%)	189 (18.1%)	34 (1.5%)	224 (21.5%)
4	55 (1.7%)	13 (0.1%)	42 (3.9%)	3 (0.1%)	52 (5%)
Hospitalized when referred for RT	354 (10.9%)	81 (3.7%)	273 (26.1%)	50 (2.3%)	304 (29.2%)
RT in patient's history	751 (23.1%)	240 (10.9%)	511 (48.8%)	259 (11.7%)	492 (47.3%)
Concomitant / Palliative Chemotherapy	995 (30.6%)	513 (23.3%)	482 (46.0%)	512 (23.2%)	483 (46.4%)

Abbreviations: s.d.: Standard deviation – y.o.: years old – ECOG-PS: Eastern Cooperative Oncology Group-Performance Status – RT: radiotherapy

[a] : All p values (between metastatic and non-metastatic disease, and between curative and palliative RT) are significant and < 0.001, except for age stratified by metastatic status (p = 0.746).

Table 1B: **Primary tumor's characteristics** : Primary cancer site (in **boldface**) and histology (in *italics*; detailed only if it represents more than 5% of observed tumors)

	Overall Population	Metastatic Status		Therapeutic Objective	
		Non-Metastatic Disease	Metastatic Disease	Curative Radiotherapy	Palliative Radiotherapy
	n = 3248 (%)	2201 (67.8%)	1047 (32.2%)	[1]2207 (67.9%)	1041 (32.1%)
BREAST	1113 (34.3%)	925 (42.0%)	188 (18.0%)	943 (42.7%)	170 (16.3%)
IDC	824 (74.0%)	667 (72.1%)	157 (83.5%)	684 (72.5%)	140 (82.3%)
ILC	149 (13.4%)	125 (13.5%)	24 (12.8%)	127 (13.5%)	22 (12.9%)
In situ DC/LC	71 (6.4%)	71 (7.7%)	0 (0.0%)	71 (7.5%)	0 (0.0%)
Other histology	69 (6.2%)	58 (6.2%)	11 (5.8%)	61 (6.5%)	8 (4.7%)
LUNG	535 (16.5%)	165 (7.5%)	370 (35.3%)	168 (7.6%)	367 (35.3%)
ADK	225 (42.1%)	40 (24.2%)	185 (50.0%)	47 (28.0%)	178 (48.5%)
SCC	128 (24.0%)	68 (41.2%)	60 (16.2%)	68 (40.5%)	60 (16.3%)
NET	114 (21.3%)	24 (14.5%)	90 (24.3%)	22 (13.1%)	92 (25.1%)
Other histology	68 (12.7%)	33 (20.0%)	35 (9.5%)	31 (18.5%)	37 (10.1%)
SKIN	72 (2.2%)	40 (1.8%)	32 (3.1%)	35 (1.6%)	37 (3.6%)
SCC	21 (29.2%)	17 (42.5%)	4 (12.5%)	11 (31.4%)	10 (27.0%)
Melanoma	29 (40.3%)	3 (7.5%)	26 (81.3%)	5 (14.3%)	24 (64.9%)
Other histology	22 (30.6.%)	20 (50.0%)	2 (6.3%)	19 (54.3%)	3 (8.1%)
DIGESTIVE ORGANS	386 (11.9%)	226 (10.3%)	160 (15.3%)	243 (11.0%)	143 (13.7%)
Esophagus	95 (24.6%)	80 (35.4%)	15 (9.3%)	72 (29.6%)	23 (16%)
SCC	65 (68.4%)	55 (68.8%)	10 (66.7%)	50 (69.4%)	15 (65.2%)
ADK	26 (27.4%)	22 (27.5%)	4 (26.7%)	21 (29.2%)	5 (21.7%)
Rectum and anal canal	179 (46.3%)	128 (56.6%)	51 (31.8%)	148 (60.9%)	31 (21.6%)
ADK	151 (84.4%)	108 (84.4%)	43 (84.3%)	122 (82.4%)	29 (93.5%)
SCC	20 (11.2%)	15 (11.7%)	5 (9.8%)	19 (12.8%)	1 (3.2%)
Liver, pancreas, bile ducts	46 (11.9%)	11 (4.8%)	35 (21.8%)	13 (5.3%)	33 (23%)
ADK	22 (47.8%)	9 (81.8%)	13 (37.1%)	10 (76.9%)	12 (36.4%)
Other histology	24 (52.2%)	2 (18.2%)	22 (62.9%)	3 (23.1%)	21 (63.6%)
HEAD AND NECK	370 (11.4%)	325 (14.8%)	45 (4.3%)	301 (13.6%)	69 (6.6%)
SCC	304 (82.2%)	266 (81.8%)	38 (84.4%)	246 (81.7%)	58 (84.1%)
Other histology	66 (17.8%)	59 (18..2%)	7 (15.6%)	55 (18.3%)	11 (15.9%)
Oral cavity	95 (25.7%)	81 (24.9%)	14 (0.3%)	74 (24.6%)	21 (30.4%)
Tonsils and salivary glands	47 (12.7%)	40 (12.3%)	7 (0.2%)	39 (12.9%)	8 (11.6%)
Larynx	62 (16.7%)	56 (17.2%)	6 (0.1%)	52 (17.3%)	10 (14.5%)
Naso- and oropharynx	48 (12.9%)	45 (13.8%)	3 (< 0.1%)	41 (13.6%)	7 (10.1%)

Face sinuses	42 (11.3%)	37 (11.3%)	5 (0.1%)	33 (10.9%)	9 (13%)
Piriform sinus and hypopharynx	63 (17%)	54 (16.6%)	9 (0.2%)	51 (16.9%)	12 (17.4%)
GYNECOLOGICAL	206 (6.3%)	166 (7.5%)	40 (3.8%)	156 (7.1%)	50 (4.8%)
ADK	34 (16.5%)	26 (15.7%)	8 (20.0%)	25 (16.0%)	9 (18.0%)
SCC	74 (35.9%)	64 (38.6%)	10 (25.0%)	60 (38.5%)	14 (28.0%)
Endometroid carcinoma	52 (25.2%)	46 (27.7%)	6 (15.0%)	44 (28.2%)	8 (16.0%)
Other histology	46 (22.3%)	30 (18.1%)	16 (40.0%)	27 (17.3%)	19 (38.0%)
Corpus uteri	97 (47%)	81 (48.8%)	16 (40%)	76 (48.7%)	21 (42%)
Cervix uteri	68 (33%)	60 (36.2%)	8 (20%)	58 (37.2%)	10 (20%)
Other gynecological site	41 (20%)	25 (15%)	16 (40%)	22 (14.1%)	19 (38%)
KIDNEY	58 (1.8%)	1 (<0.1%)	57 (5.4%)	4 (0.2%)	54 (5.2%)
Renal cell carcinoma	55 (94.8%)	0 (0.0%)	55 (96.5%)	4 (100%)	51 (94.4%)
MESOTHELIAL TISSUE	90 (2.8%)	73 (3.3%)	17 (1.6%)	72 (3.3%)	18 (1.7%)
Sarcoma	90 (100.0%)	73 (100%)	17 (100%)	72 (100%)	18 (100%)
CENTRAL NERVOUS SYSTEM	135 (4.2%)	129 (5.9%)	6 (0.6%)	125 (5.7%)	10 (1.0%)
Brain	121 (89.6%)	120 (93%)	1 (16.6%)	115 (92%)	6 (0.6%)
Glioblastoma	74 (61.2%)	73 (60.8%)	1 (100.0%)	70 (60.9%)	4 (66.7%)
Other histology	47 (38.8%)	47 (39.2%)	0 (0.0%)	45 (39.1%)	2 (33.3%)
PROSTATE	177 (5.4%)	121 (5.5%)	56 (5.3%)	130 (5.9%)	47 (4.5%)
ADK	175 (99%)	120 (99.2%)	55 (98.2%)	129 (99.2%)	46 (97.9%)
OTHER PRIMARY TYPE	106 (3.2%)	30 (1.4%)	76 (7.3%)	30 (1.4%)	76 (7.3%)

Abbreviations: IDC: infiltrative ductal carcinoma – ILC: infiltrative lobular carcinoma – DC: ductal carcinoma – LC: lobular carcinoma – ADK: adenocarcinoma – SCC: squamous cell carcinoma – NET: neuroendocrine tumor

Table 1C: Metastatic sites

	Overall Population	Metastatic Status		Therapeutic Objective	
		Non-Metastatic Disease	Metastatic Disease	Curative Radiotherapy	Palliative Radiotherapy
	n = 3248 (%)	2201 (67.8%)	1047 (32.2%)	2207 (67.9%)	1041 (32.1%)
METASTATIC SITES					
Bones	545 (16.8%)	-	545 (52.1%)	34 (1.5%)	511 (49.1%)
Brain	459 (14.1%)	-	459 (43.8%)	10 (0.5%)	449 (43.1%)
Lung	325 (10.0%)	-	325 (31.0%)	47 (2.1%)	278 (26.7%)
Liver	256 (7.9%)	-	256 (24.5%)	25 (1.1%)	231 (22.2%)
Distant nodes	192 (5.9%)	-	192 (18.3%)	22 (1.0%)	170 (16.3%)
Adrenal glands	93 (2.9%)	-	93 (8.9%)	5 (0.2%)	88 (8.5%)
Skin (and muscle)	65 (2%)	-	65 (6.2%)	7 (0.3%)	58 (5.6%)
Serosa (pleura, peritoneum)	50 (1.5%)	-	50 (4.8%)	0 (0.0%)	50 (4.8%)
Other	50 (1.5%)	-	50 (4.8%)	7 (0.3%)	43 (4.1%)

All p values (between metastatic and non-metastatic disease, and between curative and palliative RT) are significant and < 0.001.

Table 1D: Radiotherapy's characteristics

	Overall Population	Metastatic Status		Therapeutic Objective	
		Non-Metastatic Disease	Metastatic Disease	Curative Radiotherapy	Palliative Radiotherapy
	n = 3248 (%)	2201 (67.8%)	1047 (32.2%)	2207 (67.9%)	1041 (32.1%)
RADIOTHERAPY'S CHARACTERISTICS					
Radiotherapy duration (days, mean (s.d.))		40.5 (13.4)	12.8 (10.6)	40.8 (13.0)	12.1 (9.8)
Technics					
3D-CRT	2253 (69.4%)	1508 (68.5%)	745 (71.2%)	1444 (65.4%)	809 (77.7%)
IMRT	621 (19.1%)	581 (26.4%)	40 (3.8%)	588 (26.6%)	33 (3.2%)
SRT	374 (11.5%)	112 (5.1%)	262 (25.0%)	175 (7.9%)	199 (19.1%)
Dose (Gy, mean (s.d.))	47.2 (17.2)	55.6 (12.3)	29.6 (11.8)	56.1 (11.5)	28.2 (10.4)
Fractions (mean (s.d.))	20.4 (11.7)	26.2 (8.8)	8.4 (7.0)	26.3 (8.8)	8.1 (6.3)
Dose per fraction (Gy, mean (s.d.))	3.5 (3.1)	2.5 (1.6)	5.6 (4.3)	2.6 (1.9)	5.4 (4.2)
No Completion of RT	135 (4.2%)	63 (2.9%)	72 (6.9%)	47 (2.1%)	88 (8.5%)

- Abbreviations: s.d.: Standard deviation – 3D-CRT: 3-dimensional conformational radiation therapy – IMRT: intensity-modulated radiotherapy – SRT: stereotactic radiation therapy – Gy: Gray

- All p values (between metastatic and non-metastatic disease, and between curative and palliative RT) are significant and < 0.001.

Table 1E: Treated sites

	Overall Population	Metastatic Status		Therapeutic Objective	
		Non-Metastatic Disease	Metastatic Disease	Curative Radiotherapy	Palliative Radiotherapy
	n = 3248 (%)	2201 (67.8%)	1047 (32.2%)	2207 (67.9%)	1041 (32.1%)
TREATED SITE					
Brain	527 (16.2%)	135 (6.1%)	392 (37.4%)	133 (6.0%)	394 (37.8%)
WBRT for brain metastasis	243 (7.5%)	12 (0.5%)	231 (22.1%)	13 (0.6%)	230 (22.1%)
SRT for brain metastasis	160 (4.9%)	0 (0.0%)	160 (15.3%)	2 (0.1%)	158 (15.2%)
Primitive brain tumor	120 (3.7%)	120 (5.5%)	0 (0.0%)	115 (5.2%)	5 (0.5%)
Head and Neck	413 (12.7%)	373 (16.9%)	40 (3.8%)	344 (15.6%)	69 (6.6%)
Breast or Chest Wall	1010 (31.1%)	936 (42.5%)	74 (7.1%)	948 (43.0%)	62 (6.0%)
Intrathoracic					
Lung	184 (5.7%)	133 (6.0%) [a]	51 (4.9%) [a]	149 (6.8%)	35 (3.4%)
Esophagus	80 (2.5%)	74 (3.4%)	6 (0.6%)	65 (2.9%)	15 (1.4%)
Mediastinum	53 (1.6%)	28 (1.3%)	25 (2.4%)	26 (1.2%)	27 (2.6%)
Abdominal					
Pancreas	9 (0.3%)	7 (0.3%) [a]	2 (0.2%) [a]	7 (0.3%) [b]	2 (0.2%) [b]
Liver	6 (0.2%)	2 (0.1%) [a]	4 (0.4%) [a]	3 (0.1%) [b]	3 (0.3%) [b]
Other abdominal site	45 (1.4%)	22 (1.0%)	23 (2.2%)	24 (1.1%) [b]	21 (2.0%) [b]
Pelvis					
Rectum and anal canal	174 (5.4%)	128 (5.8%) [a]	46 (4.4%) [a]	140 (6.3%)	34 (3.3%)
Gynecological	170 (5.2%)	159 (7.2%)	11 (1.1%)	147 (6.7%)	23 (2.2%)
Prostate	123 (3.8%)	121 (5.5%)	2 (0.2%)	120 (5.4%)	3 (0.3%)
Other pelvic site	105 (3.2%)	24 (1.1%)	81 (7.7%)	29 (1.3%)	76 (7.3%)
Bones					
Rachis	243 (7.5%)	12 (0.5%)	231 (22.1%)	24 (1.1%)	219 (21.0%)
Bones (other than vertebras)	188 (5.8%)	10 (0.5%)	178 (17.0%)	18 (0.8%)	170 (16.3%)
Limbs	108 (3.3%)	37 (1.7%)	71 (6.8%)	42 (1.9%)	66 (6.3%)
Other sites	39 (1.2%)	17 (0.8%)	22 (2.1%)	15 (0.7%)	24 (2.3%)

Abbreviations: WBRT: whole brain radiation therapy – SRT: stereotactic radiation therapy

[a, b] : Non-significant p values ([a] : between metastatic and non-metastatic disease, and [b]: between curative and palliative RT); all the other ones are significant and < 0.05

Table 2: Characteristics of patients deceased in the 7 days, 30 days, 60 days, 6 months and one year after radiotherapy

	Deceased at 7 days	Deceased at 30 days	Deceased at 60 days	Deceased at 6 months	Deceased at 1 year
n = 3248 (%)	84 (2.6%)	234 (7.2%)	381 (11.7%)	699 (21.5%)	950 (29.2%)
PATIENTS' CHARACTERISTICS					
Sex = Female	36 (42.9%%)	101 (43.2%)	164 (43.0%)	308 (44.1%)	403 (42.4%)
Age (mean (s.d.))	63.75 (14.25)	64.23 (13.23)	64.70 (12.84)	64.97 (12.40)	65.35 (12.35)
ECOG-PS 0	2 (2.4%)	8 (3.4%)	13 (3.4%)	34 (4.9%)	65 (6.8%)
1	17 (20.2%)	47 (20.1%)	86 (22.6%)	216 (30.9%)	338 (35.6%)
2	19 (22.6%)	68 (29.1%)	121 (31.8%)	228 (32.6%)	295 (31.1%)
3	39 (46.4%)	85 (36.3%)	125 (32.8%)	176 (25.2%)	203 (21.4%)
4	7 (8.3%)	26 (11.1%)	36 (9.4%)	45 (6.4%)	49 (5.2%)
Hospitalized when referred for RT	47 (56.0%)	113 (48.3%)	173 (45.4%)	237 (33.9%)	273 (28.7%)
RT in patient's history	25 (29.8%)	88 (37.6%)	153 (40.2%)	278 (39.8%)	367 (38.6%)
Concomitant / Palliative Chemotherapy	33 (39.3%)	110 (47.0%)	188 (49.3%)	335 (47.9%)	447 (47.1%)
RADIOTHERAPY CHARACTERISTICS					
Radiotherapy duration (mean (s.d.))	10.4 (11.3)	12 (11.8)	12.8 (12)	15.6 (14.4)	18.2 (16)
Prescribed dose (mean (s.d.))	32.2 (15.8)	29.9 (14.7)	29.9 (14.2)	32.1 (15.3)	34.5 (16.3)
Number of fractions (mean (s.d.))	12.1 (9.3)	10.1 (8.5)	9.9 (8.5)	10.9 (9.5)	12.1 (10.2)
Dose per fraction (mean (s.d.))	3.6 (1.7)	4.4 (3.1)	4.5 (3.3)	4.7 (3.7)	4.7 (3.8)
PRIMARY TUMOR'S CHARACTERISTICS					
Breast	5 (6.0%)	21 (9.0%)	34 (8.9%)	75 (10.7%)	101 (10.6%)
Lung	29 (34.5%)	77 (32.9%)	127 (33.3%)	228 (32.6%)	300 (31.6%)
Digestive organs	14 (16.7%)	48 (20.5%)	69 (18.1%)	110 (15.7%)	151 (15.9%)
Esophagus	5 (6.0%)	13 (5.6%)	19 (5.0%)	34 (4.9%)	51(5.4%)
Rectum and anal canal	1 (1.2%)	7 (3.0%)	11 (2.9%)	18 (2.6%)	27 (2.8%)
Head and Neck	13 (15.5%)	28 (12.0%)	38 (10.0%)	85 (12.2%)	128 (13.5%)
Oral cavity	4 (4.8%)	9 (3.8%)	11 (2.9%)	26 (3.7%)	35 (3.7%)
Tonsils and salivary glands	1 (1.2%)	1 (0.4%)	2 (0.5%)	9 (1.3%)	15 (1.6%)
Larynx	1 (1.2%)	3 (1.3%)	5 (1.3%)	9 (1.3%)	18 (1.9%)
Naso- and oropharynx	2 (2.4%)	4 (1.7%)	4 (1.0%)	12 (1.7%)	16 (1.7%)
Face sinuses	0 (0%)	2 (0.9%)	4 (1.0%)	11 (1.6%)	11 (1.2%)
Piriform sinus and hypopharynx	3 (3.6%)	7 (3.0%)	9 (2.4%)	15 (2.1%)	29 (3.1%)
Gynecological	6 (7.1%)	11 (4.7%)	19 (5.0%)	34 (4.9%)	52 (5.5%)
Cervix uteri	2 (2.4%)	4 (1.7%)	6 (1.6%)	9 (1.3%)	14 (1.5%)
Corpus uteri	1 (1.2%)	4 (1.7%)	6 (1.6%)	10 (1.4%)	19 (2.0%)
Skin	1 (1.2%)	7 (3.0%)	16 (4.2%)	25 (3.6%)	35 (3.7%)
Prostate	1 (1.2%)	3 (1.3%)	9 (2.4%)	19 (2.7%)	27 (2.8%)
Kidney	1 (1.2%)	7 (3.0%)	14 (3.7%)	26 (3.7%)	34 (3.6%)
Central nervous system	3 (3.6%)	6 (2.6%)	13 (3.4%)	32 (4.6%)	49 (5.2%)
Mesothelial tissue	2 (2.4%)	5 (2.1%)	7 (1.8%)	13 (1.9%)	14 (1.5%)

METASTATIC SITES					
Metastatic Disease	59 (70.2%)	179 (76.5%)	298 (78.2%)	507 (72.5%)	624 (65.7%)
Number of metastasis (mean (s.d.))	1.85 (1.62)	1.82 (1.47)	1.79 (1.45)	1.61 (1.41)	1.41 (1.39)
Brain	26 (31.0%)	78 (33.3%)	139 (36.5%)	252 (36.1%)	304 (32.0%)
Bone	39 (46.4%)	118 (50.4%)	187 (49.1%)	296 (42.3%)	345 (36.3%)
Liver	25 (29.8%)	69 (29.5%)	101 (26.5%)	150 (21.5%)	176 (18.5%)
Lung	24 (28.6%)	59 (25.2%)	100 (26.2%)	165 (23.6%)	199 (20.9%)
Distant nodes	16 (19.0%)	46 (19.7%)	65 (17.1%)	107 (15.3%)	124 (13.1%)
Adrenal glands	10 (11.9%)	21 (9.0%)	33 (8.7%)	55 (7.9%)	68 (7.2%)
Skin (and muscle)	5 (6.0%)	9 (3.8%)	15 (3.9%)	30 (4.3%)	39 (4.1%)
Serosa (pleura, peritoneum)	5 (6.0%)	13 (5.6%)	20 (5.2%)	30 (4.3%)	40 (4.2%)
TREATED SITE					
Brain	22 (26.2%)	66 (28.2%)	127 (33.3%)	238 (34.0%)	306 (32.2%)
WBRT for brain metastasis	19 (22.6%)	49 (20.9%)	91 (23.9%)	144 (20.6%)	170 (17.9%)
Primitive brain tumor	3 (3.6%)	5 (2.1%)	10 (2.6%)	27 (3.9%)	45 (4.7%)
SRT for brain metastasis	0 (0%)	12 (5.1%)	26 (6.8%)	67 (9.6%)	90 (9.5%)
Bones					
Rachis	22 (26.2%)	54 (23.1%)	83 (21.8%)	136 (19.5%)	155 (16.3%)
Bones (other than vertebras)	12 (14.3%)	34 (14.5%)	55 (14.4%)	78 (11.2%)	104 (10.9%)
Head and Neck	13 (15.5%)	30 (12.8%)	43 (11.3%)	89 (12.7%)	133 (14.0%)
Intrathoracic					
Lung and Mediastinum	5 (6.0%)	20 (8.5%)	29 (7.6%)	51 (7.3%)	80 (8.4%)
Esophagus	5 (6.0%)	8 (3.4%)	12 (3.1%)	26 (3.7%)	41 (4.3%)
Abdominal	3 (3.6%)	8 (3.4%)	9 (2.4%)	20 (2.9%)	24 (2.5%)
Pelvis	3 (3.6%)	13 (5.6%)	18 (4.7%)	26 (3.7%)	46 (4.8%)
Rectum and anal canal	0 (0%)	6 (2.6%)	8 (2.1%)	19 (2.7%)	28 (2.9%)
Prostate	0 (0%)	0 (0%)	1 (0.3%)	2 (0.3%)	5 (0.5%)
Gynecological	4 (4.8%)	6 (2.6%)	10 (2.6%)	20 (2.9%)	34 (3.6%)
Breast or Chest Wall	3 (3.6%)	10 (4.3%)	21 (5.5%)	41 (5.9%)	56 (5.9%)
Limbs	5 (6.0%)	16 (6.8%)	25 (6.6%)	36 (5.2%)	46 (4.8%)

Abbreviations: s.d.: Standard deviation – ECOG-PS: Eastern Cooperative Oncology Group- Performance Status – RT: radiotherapy – SRT: stereotactic radiation therapy – WBRT: whole brain radiation therapy

Table 3 : Patients deceased in the 7 days, 30 days, 60 days, 6 months and one year after radiotherapy, stratified by Metastatic Disease and Treatment's Objective

	Metastatic Status		Treatment's Objective		Metastatic Disease & Palliative RT	Overall Population
	Non-Metastatic Disease	Metastatic Disease	Curative Radiotherapy	Palliative Radiotherapy		
Deceased at 7 days	25 (29.8%)	59 (70.2%)	15 (17.8%)	69 (82.2%)	58 (69%)	84
Deceased at 30 days	55 (23.5%)	179 (76.5%)	35 (14.9%)	199 (85.1%)	177 (75.6%)	234
Deceased at 60 days	83 (21.8%)	298 (78.2%)	55 (14.4%)	326 (85.6%)	294 (77.2%)	381
Deceased at 6 months	192 (27.5%)	507 (72.5%)	142 (20.3%)	557 (79.7%)	497 (71.1%)	699
Deceased at 1 year	326 (34.3%)	624 (65.7%)	263 (27.7%)	687 (72.3%)	607 (63.9%)	950

	Deceased at 7 days	Deceased at 30 days	Deceased at 60 days	Deceased at 6 months	Deceased at 1 year	Overall Population
Non-Metastatic Disease	25 (1.1%)	55 (2.5%)	83 (3.8%)	192 (8.7%)	326 (14.8%)	2201
Metastatic Disease	59 (5.6%)	179 (17.1%)	298 (28.5%)	507 (48.4%)	624 (59.6%)	1047
Curative Radiotherapy	15 (0.7%)	35 (1.6%)	55 (2.5%)	142 (6.4%)	263 (11.9%)	2207
Palliative Radiotherapy	69 (6.6%)	199 (19.1%)	326 (31.3%)	557 (53.5%)	687 (66.0%)	1041
Metastatic Disease & Palliative RT	58 (6.2%)	177 (19.1%)	294 (31.6%)	497 (53.5%)	607 (65.3%)	929
Overall Population	84 (2.6%)	234 (7.2%)	381 (11.7%)	699 (21.5%)	950 (29.2%)	3248

Table 4: Patients with Metastatic Disease and treated with Palliative Radiotherapy: univariate survival analysis with Cox model, variables excluded by the correlation test, multivariate Cox model and final selection with stepwise regression model. The correlation tests used to optimize the multivariate analysis are visible in Supplementary Data 1.

		Univariate Analysis			Multivariate Analysis			Final Stepwise Analysis		
		p value	**HR**	**(95% CI for HR)**	**p value**	**HR**	**(95% CI for HR)**	**p value**	**HR**	**(95% CI for HR)**
Sex	*n=929*	**0.024**	0.85	0.86	0.86	0.99	(0.83-1.17)	-	-	
Age	*n=929*	**0.015**	1	(1-1)	0.60	1.00	(1.00-1.01)	-	-	
ECOG-PS	*n=929*	**< 0.001**	1.8	(1.6-1.9)	**< 0.001**	1.69	(1.55-1.85)	**< 0.001**	**1.70**	**(1.57-1.84)**
Hospitalized when referred for RT	*n=271*	**< 0.001**	2.4	(2-2.8)	*	*		*	*	
RT in patient's history	*n=450*	0.23	0.92	(0.79-1.1)	*	*		*	*	
Concomitant/Palliative Chemotherapy	*n=457*	0.055	1.2	(1-1.3)	0.32	1.08	(0.93-1.25)	-	-	
Radiotherapy's Objective										
Pain control	*n=254*	0.9	1	(0.86-1.2)	-	-		-	-	
Bleeding control	*n=25*	**0.041**	1.6	(1-2.4)	0.25	1.33	(0.82-2.16)	-	-	
Compressive symptoms	*n=57*	0.11	1.3	(0.95-1.7)	0.56	1.11	(0.78-1.59)	-	-	
Local control	*n=105*	**< 0.001**	0.65	(0.52-0.82)	0.70	1.06	(0.80-1.39)	-	-	
Symptomatic epiduritis	*n=100*	**< 0.001**	1.5	(1.2-1.9)	0.76	1.04	(0.80-1.36)	-	-	
Asymptomatic brain metastasis	*n=183*	**< 0.001**	0.67	(0.55-0.8)	0.68	1.07	(0.78-1.45	-	-	
Symptomatic brain metastasis	*n=205*	**< 0.001**	1.4	(1.2-1.7)	**< 0.001**	1.51	(1.13-2.00)	**0.001**	**1.39**	**(1.14-1.68)**
Primary Type										
Breast	*n=168*	**< 0.001**	0.6	(0.5-0.73)	**< 0.001**	0.63	(0.49-0.82)	**< 0.001**	**0.63**	**(0.50-0.80)**
Lung	*n=352*	**< 0.001**	1.3	(1.1-1.5)	**0.05**	1.24	(1.00-1.53)	**0.05**	**1.22**	**(1.00-1.49)**
Skin	*n=26*	0.44	1.2	(0.78-1.8)	-	-		-	-	
Gynecological	*n=34*	0.93	0.98	(0.67-1.4)	-	-		-	-	
Cervix uteri	*n=5*	0.79	0.88	(0.33-2.3)	-	-		-	-	
Corpus uteri	*n=14*	0.88	0.96	(0.54-1.7)	-	-		-	-	
Prostate	*n=45*	**0.022**	0.66	(0.47-0.94)	**0.02**	0.62	(0.42-0.92)	**0.01**	**0.62**	**(0.42-0.91)**
Kidney	*n=53*	0.65	0.93	(0.69-1.3)	-	-		-	-	
Head and Neck	*n=39*	0.19	1.3	(0.89-1.8)	0.76	0.93	(0.59-1.46)	-	-	
Oral cavity	*n=12*	0.16	1.6	(0.83-2.9)	*	*		*	*	
Tonsils and salivary glands	*n=7*	0.24	0.59	(0.25-1.4)	-	-		-	-	
Larynx	*n=5*	0.15	1.9	(0.8-4.6)	0.06	2.61	(0.95-7.21)	**0.03**	**2.77**	**(1.12-6.87)**
Rhino- and oropharynx	*n=3*	0.97	0.97	(0.24-3.9)	-	-		-	-	
Face sinuses	*n=4*	**0.025**	3.1	(1.2-8.3)	0.06	2.86	(0.98-8.37)	-	-	
Hypopharynx	*n=7*	0.83	1.1	(0.49-2.4)	-	-		-	-	

Brain	*n=5*	0.24	1.7	(0.7-4.1)	-	-		-	-	
Sarcoma	*n=13*	**0.081**	0.56	(0.29-1.1)	0.09	0.55	(0.28-1.11)	-	-	
Digestive organ	*n=123*	**0.004**	1.4	(1.1-1.7)	0.14	1.24	(0.94-1.63)	-	-	
Esophagus	*n=13*	**< 0.001**	2.7	(1.6-4.7)	0.06	1.89	(0.98-3.64)	**0.02**	**2.07**	**(1.13-3.78)**
Rectum and anal canal	*n=23*	0.79	0.94	(0.58-1.5)	-	-		-	-	
Metastatic Sites										
Number of metastatic sites	*n=929*	**< 0.001**	1.3	(1.2-1.3)	**0.04**	1.10	(1.00-1.21)	**0.004**	**1.11**	**(1.04-1.20)**
Brain	*n=449*	0.44	1.1	(0.92-1.2)	-	-		-	-	
Bone	*n=511*	**0.005**	1.2	(1.1-1.4)	**0.02**	1.31	(1.04-1.65)	**0.02**	**1.25**	**(1.04-1.51)**
Liver	*n=231*	**< 0.001**	1.5	(1.3-1.8)	*	*		*	*	
Lung	*n=278*	**0.02**	1.2	(1-1.4)	*	*		*	*	
Distant nodes	*n=170*	**0.01**	1.3	(1.1-1.5)	0.11	1.20	(0.96-1.51)	-	-	
Adrenal glands	*n=88*	**0.006**	1.4	(1.1-1.7)	0.88	0.98	(0.75-1.28)	-	-	
Skin. muscle	*n=45*	0.11	1.3	(0.95-1.8)	0.21	1.27	(0.87-1.85)	-	-	
Serosa	*n=50*	0.054	1.3	(1-1.8)	0.57	0.91	(0.66-1.26)	-	-	
Treated Sites										
Brain	*n=389*	0.79	0.98	(0.85-1.1)	-	-		-	-	
Brain Metastasis. WBRT	*n=230*	**< 0.001**	1.4	(1.2-1.7)	-	-		-	-	
Brain Metastasis. SRT	*n=158*	**< 0.001**	0.64	(0.53-0.79)	**0.03**	0.77	(0.60-0.98)	**0.02**	**0.77**	**(0.61-0.96)**
Rachis	*n=217*	**0.01**	1.2	(1.1-1.5)	*	*		*	*	
Bone	*n=168*	0.48	0.93	(0.77-1.1)	-	-		-	-	
Head and Neck	*n=30*	0.22	1.3	(0.87-1.9)	-	-		-	-	
Lung and Mediastinum	*n=43*	0.27	1.2	(0.86-1.7)	-	-		-	-	
Esophagus	*n=6*	0.084	2	(0.91-4.5)	0.59	1.28	(0.52-3.19)	-	-	
Abdominal	*n=23*	0.84	1	(0.66-1.7)	-	-		-	-	
Rectum and anal canal	*n=26*	0.77	0.93	(0.6-1.5)	-	-		-	-	
Pelvis	*n=70*	0.088	0.78	(0.59-1)	**0.01**	0.68	(0.50-0.92)	**0.01**	**0.67**	**(0.50-0.90)**
Prostate	*n=1*	0.78	0.76	(0.11-5.4)	-	-		-	-	
Gynecological	*n=9*	0.25	1.5	(0.76-2.8)	-	-		-	-	
Breast. chest wall	*n=58*	**0.005**	0.63	(0.46-0.87)	0.17	0.78	(0.55-1.11)	-	-	
Limb	*n=65*	0.39	1.1	(0.85-1.5)	-	-		-	-	

* : Variable with significant p value < 0.05 in univariate analysis, but discarded by correlation test (cf figures 9 and 10)

Abbreviations: ECOG-PS: Eastern Cooperative Oncology Group- Performance Status – RT: radiotherapy – WBRT: whole brain radiation therapy – SRT: stereotactic radiation therapy

Table 5 : Patients with Metastatic Disease and treated with Palliative Radiotherapy (n = 929) deceased at 7 days, 30 days and 60 days after radiotherapy: univariate survival analysis with Cox model, variables excluded by the correlation test, multivariate Cox model and final selection with stepwise regression models.
Only variables with significant p value < 0.20 in univariate analysis are displayed below.
The correlation tests used to optimize the multivariate analysis are visible in Supplementary Data 2.

		Univariate Analysis			Multivariate Analysis			Final Stepwise Analysis		
		p value	HR	(95% CI for HR)	p value	HR	(95% CI for HR)	p value	HR	(95% CI for HR)
DECEASED AT 7 DAYS	*n=58*									
ECOG - PS	*n=58*	**< 0.001**	2,4	(1,8 - 3)	**< 0.001**	2,03	(1,53 - 2,69)	**< 0.001**	**2,28**	**(1,74 - 2,98)**
Hospitalized when referred for RT	*n=47*	**< 0.001**	5,3	(3,1 - 9,3)	*	*	*	*	*	*
RT in patient's history	*n=25*	**0,026**	0,54	(0,31 - 0,93)	**0,03**	0,53	(0,30 - 0,95)	**0,01**	**0,49**	**(0,28 -0,84)**
Concomitant/Palliative Chemotherapy	*n=33*	0,12	0,66	(0,39 - 1,1)	**0,02**	0,53	(0,31 - 0,91)	**0,03**	**0,55**	**(0,32 -0,93)**
Radiotherapy's Objective										
Compressive symptoms	*n=7*	0,064	2,1	(0,96 - 4,7)	**0,04**	2,93	(1,07 - 8,02)	**0,04**	**2,36**	**(1,06 -5,28)**
Symptomatic epiduritis	*n=14*	**0,001**	2,7	(1,5 - 5)	0,21	1,77	(0,72 - 4,33)	-	-	-
Asymptomatic Brain Metastasis	*n=2*	**0,006**	0,14	(0,034 - 0,57)	*	*	*	*	*	*
Primary Type										
Breast	*n=5*	0,063	0,42	(0,17 - 1)	0,61	0,77	(0,29 - 2,08)	-	-	-
Lung	*n=27*	0,15	1,5	(0,87 - 2,4)	0,14	1,55	(0,86 - 2,78)	-	-	-
Metastatic Sites										
Number of metastatic sites	*n=58*	**< 0.001**	1,5	(1,3 - 1,9)	**0,01**	1,41	(1,07 - 1,87)	**< 0.001**	**1,48**	**(1,21 -1,80)**
Bone	*n=39*	0,059	1,7	(0,98 - 2,9)	1,00	1,00	(0,47 - 2,11)	-	-	-
Liver	*n=25*	**0,001**	2,3	(1,4 - 3,9)	-	-	-	-	-	-
Lung	*n=24*	0,052	1,7	(1 - 2,8)	-	-	-	-	-	-
Distant nodes	*n=15*	0,12	1,6	(0,88 - 2,9)	0,62	1,18	(0,60 - 2,32)	-	-	-
Adrenal glands	*n=10*	**0,042**	2	(1 - 4)	0,65	1,20	(0,54 - 2,66)	-	-	-
Skin, muscle	*n=5*	0,17	1,9	(0,76 - 4,8)	0,82	1,13	(0,39 - 3,29)	-	-	-
Treated Sites										
Rachis	*n=22*	**0,008**	2	(1,2 - 3,5)	0,33	1,58	(0,63 - 3,92)	-	-	-

DECEASED AT 30 DAYS	*n=177*											
ECOG - PS	*n=177*	**< 0.001**	2,2	(1,9 - 2,5)	**< 0.001**	2,13	(1,82	- 2,49)	**< 0.001**	**2,16**	**(1,85**	**-2,52)**
Hospitalized when referred for RT	*n=92*	**< 0.001**	3,2	(2,4 - 4,3)	*	*	*		*	*	*	
RT in patient's history	*n=76*	0,076	0,76	(0,57 - 1)	0,20	0,81	(0,59	- 1,12)	-	-	-	
Radiotherapy's Objective												
Compressive symptoms	*n=17*	**0,030**	1,7	(1,1 - 2,9)	0,56	1,22	(0,62	- 2,41)	-	-	-	
Local control	*n=13*	0,072	0,59	(0,34 - 1)	0,99	1,00	(0,54	- 1,84)	-	-	-	
Symptomatic epiduritis	*n=28*	**0,010**	1,7	(1,1 - 2,5)	0,44	1,20	(0,76	- 1,90)	-	-	-	
Asymptomatic Brain Metastasis	*n=15*	**< 0.001**	0,34	(0,2 - 0,57)	*	*	*		*	*	*	
Primary Type												
Breast	*n=21*	**0,018**	0,58	(0,37 - 0,91)	0,14	0,69	(0,42	- 1,13)	-	-	-	
Prostate	*n=3*	**0,048**	0,32	(0,1 - 0,99)	**0,03**	0,28	(0,09	- 0,91)	**0,03**	**0,27**	**(0,09**	**-0,88)**
Hypopharynx	*n=3*	0,11	2,5	(0,81 - 7,9)	**0,03**	3,70	(1,14	- 11,99)	**0,04**	**3,30**	**(1,04**	**-10,46)**
Digestive organ	*n=36*	**0,002**	1,8	(1,2 - 2,6)	**0,02**	1,63	(1,08	- 2,48)	**0,005**	**1,74**	**(1,19**	**-2,54)**
Esophagus	*n=6*	**0,011**	2,9	(1,3 - 6,5)	0,48	1,40	(0,56	- 3,48)	-	-	-	
Metastatic Sites												
Number of metastatic sites	*n=177*	**< 0.001**	1,3	(1,2 - 1,5)	0,06	1,15	(0,99	- 1,32)	**0,05**	**1,14**	**(1,00**	**-1,29)**
Bone	*n=117*	**0,001**	1,7	(1,2 - 2,3)	**0,05**	1,51	(0,99	- 2,29)	**0,03**	**1,45**	**(1,04**	**-2,04)**
Liver	*n=69*	**< 0.001**	2,1	(1,6 - 2,8)	*	*	*		*	*	*	
Distant nodes	*n=45*	**0,006**	1,6	(1,1 - 2,2)	0,17	1,33	(0,89	- 1,99)	-	-	-	
Serosa	*n=13*	0,180	1,5	(0,84 - 2,6)	0,90	1,04	(0,58	- 1,86)	-	-	-	
Treated Sites												
Brain	*n=61*	**0,025**	0,7	(0,51 - 0,96)	0,64	1,11	(0,72	- 1,71)				
Brain Metastasis, SRT	*n=12*	**< 0.001**	0,31	(0,17 - 0,56)	*	*	*		*	*	*	
Rachis	*n=53*	**0,017**	1,5	(1,1 - 2)	*	*	*		*	*	*	
Lung and Mediastinum	*n=13*	0,064	1,7	(0,97 - 3)	0,08	1,98	(0,93	- 4,23)	**0,01**	**2,16**	**(1,17**	**-3,97)**

DECEASED AT 60 DAYS	*n=294*											
ECOG - PS	*n=294*	**< 0.001**	2	(1,8 - 2,3)	**< 0.001**	1,69	(1,55	- 1,85)	**< 0.001**	**1,88**	**(1,66**	**-2,12)**
Hospitalized when referred for RT	*n=147*	**< 0.001**	3,3	(2,6 - 4,1)	*	*	*		*	*	*	
Concomitant/Palliative Chemotherapy	*n=157*	0,190	1,2	(0,93 - 1,5)	0,32	1,08	(0,93	- 1,25)	-	-	-	
Radiotherapy's Objective												
Compressive symptoms	*n=24*	**0,05**	1,5	(1 - 2,3)	0,56	1,11	(0,78	- 1,59)	-	-	-	
Local control	*n=23*	**0,022**	0,61	(0,4 - 0,93)	0,70	1,06	(0,80	- 1,39)	-	-		
Symptomatic epiduritis	*n=43*	**0,004**	1,6	(1,2 - 2,2)	0,76	1,04	(0,80	- 1,36)	-	-	-	
Asymptomatic Brain Metastasis	*n=31*	**< 0.001**	0,41	(0,28 - 0,59)	0,68	1,07	(0,78	- 1,45)	-	-	-	
Symptomatic Brain Metastasis	*n=84*	**0,001**	1,5	(1,2 - 2)	**0,005**	1,51	(1,13	- 2,30)	**0,002**	**1,58**	**(1,18**	**-2,12)**
Primary Type												
Breast	*n=33*	**< 0.001**	0,52	(0,36 - 0,75)	**0,001**	0,63	(0,49	- 0,82)	**< 0.001**	**0,48**	**(0,33**	**-0,70)**
Prostate	*n=8*	**0,046**	0,49	(0,24 - 0,99)	**0,02**	0,62	(0,42	- 0,92)	**0,01**	**0,38**	**(0,19**	**-0,79)**
Larynx	*n=3*	0,200	2,1	(0,68 - 6,6)	0,06	2,61	(0,95	- 7,21)	-	-	-	
Face sinuses	*n=3*	0,098	2,6	(0,84 - 8,2)	0,06	2,86	(0,98	- 8,37)	-	-	-	
Digestive organ	*n=53*	**0,002**	1,6	(1,2 - 2,2)	0,14	1,24	(0,94	- 1,63)	-	-	-	
Esophagus	*n=9*	**0,001**	3	(1,6 - 5,9)	0,06	1,89	(0,98	- 3,64)	**0,003**	**2,76**	**(1,48**	**-5,41)**
Metastatic Sites												
Number of metastatic sites	*n=294*	**< 0.001**	1,3	(1,2 - 1,4)	**0,04**	1,10	(1,00	- 1,21)	**0,05**	**1,11**	**(1,03**	**-1,22)**
Bone	*n=186*	**< 0.001**	1,5	(1,2 - 1,9)	**0,02**	1,31	(1,04	- 1,65)	**0,01**	**1,48**	**(1,11**	**-1,96)**
Liver	*n=100*	**< 0.001**	1,8	(1,4 - 2,3)	*	*	*		*	*	*	
Lung	*n=100*	**0,052**	1,3	(1 - 1,6)	*	*	*		*	*	*	
Distant nodes	*n=64*	**0,041**	1,3	(1 - 1,8)	0,11	1,20	(0,96	- 1,51)	-	-	-	
Serosa	*n=20*	0,180	1,4	(0,86 - 2,1)	0,57	0,91	(0,66	- 1,26)	-	-	-	
Treated Site												
Brain Metastasis, WBRT	*n=91*	**0,002**	1,5	(1,2 - 1,9)	*	*	*		*	*	*	
Brain Metastasis, SRT	*n=26*	**< 0.001**	0,4	(0,27 - 0,59)	**0,03**	0,77	(0,60	- 0,98)	**0,01**	**0,58**	**(0,38**	**-0,88)**
Rachis	*n=82*	**0,017**	1,4	(1,1 - 1,8)	*	*	*		*	*	*	
Pelvis	*n=16*	0,150	0,69	(0,42 - 1,1)	**0,01**	0,68	(0,50	- 0,92)	**0,03**	**0,57**	**(0,34**	**-0,95)**

* : Variable with significant p value < 0.05 in univariate analysis, but discarded by correlation test (cf figures 9 and 10)

Abbreviations: ECOG-PS: Eastern Cooperative Oncology Group- Performance Status – RT: radiotherapy – WBRT: whole brain radiation therapy – SRT: stereotactic radiation therapy

Table 6: Patients with Metastatic Disease and treated with Palliative Radiotherapy – Prognostic Factors with an impact on observed survival and proposition of prognostic value based upon aspect of survival curves, HR value, clinical relevance

Prognostic value:
- - : Important protective factor
- : Protective factor
o: None
+: Risk factor
++ : Important risk factor

ECOG-PS	Observed categories	**0 or 1**	**2**	**3**		**4**
	Prognostic value	**-**	**o**	**+**		**++**
		Hazard Ratio (HR)	*Death at 7 days (D7): 2.28 (1.74-2.98)* *Death at 30 days (D30): 2.16 (1.85-2.52)* *Death at 60 days (D60): 1.88 (1.66-2.12)*			
Metastatic Sites	Observed categories	**1 site**	**2 sites**	**3 or 4 sites**		**5 sites or more**
	Prognostic value	**-**	**o**	**+**		**++**
			HR D7: 1.48 (1.21-1.80) *HR D30: 1.14 (1.00-1.29)* *HR D60: 1.11 (1.03-1.22)*			
Primary Type	Observed categories	**Breast**	**Prostate**	**Digestive Organs** [a]	**Hypopharynx**	**Esophagus**
	Prognostic value	**-**	**-**	**+**	**++**	**++**
		HR D60: 0.46 (0.33-0.70)	*HR D30: 0.27 (0.09-0.88)* *HR D60: 0.38 (0.19-0.79)*	*HR D30: 1.74 (1.19-2.54)*	*HR D30: 3.30 (1.04-10.46)*	*HR D60: 2.76 (1.48-5.41)*
Treated Site	Observed categories	**Asymptomatic Brain Metastasis treated with SRT** [b]		**Compressive Mediastinal Loc** [c]		
	Prognostic value	**- -**		**+ +**		
		/		/		

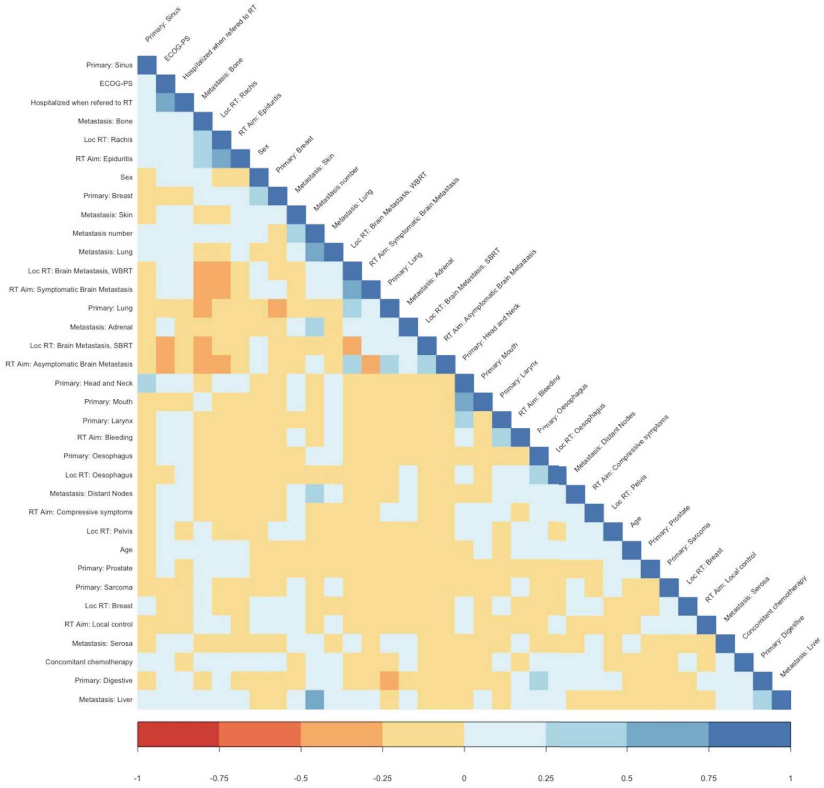
[a] : other than esophagus, rectum and anal canal
[b] : this category being construct with the opposition of the good prognostic value of SRT to the bad prognostic value of symptomatic brain metastasis, no HR was calculated
[c] : this category being construct with both bad prognostic values of referring for compressive symptoms and treatment for mediastinal localization, the opposition of the good prognostic value of SRT to the bad prognostic value of symptomatic brain metastasis, no HR was calculated

SUPPLEMENTARY DATA

Supplementary Data 1: Patients with Metastatic Disease and treated with Palliative Radiotherapy (n = 929): correlation test results for survival, for variables with significant p value < 0.20 in univariate analysis.
R value: correlation coefficient between variables 1 and 2 (significant I > 0.5 or < -0.5).
R^2: part of the variance in the variable 1 which can be explained by variation in the variable 2.
All correlations displayed below are significant (p < 0.001).

Overall Population (Metastatic Disease, Palliative Radiotherapy)

Correlation matrix

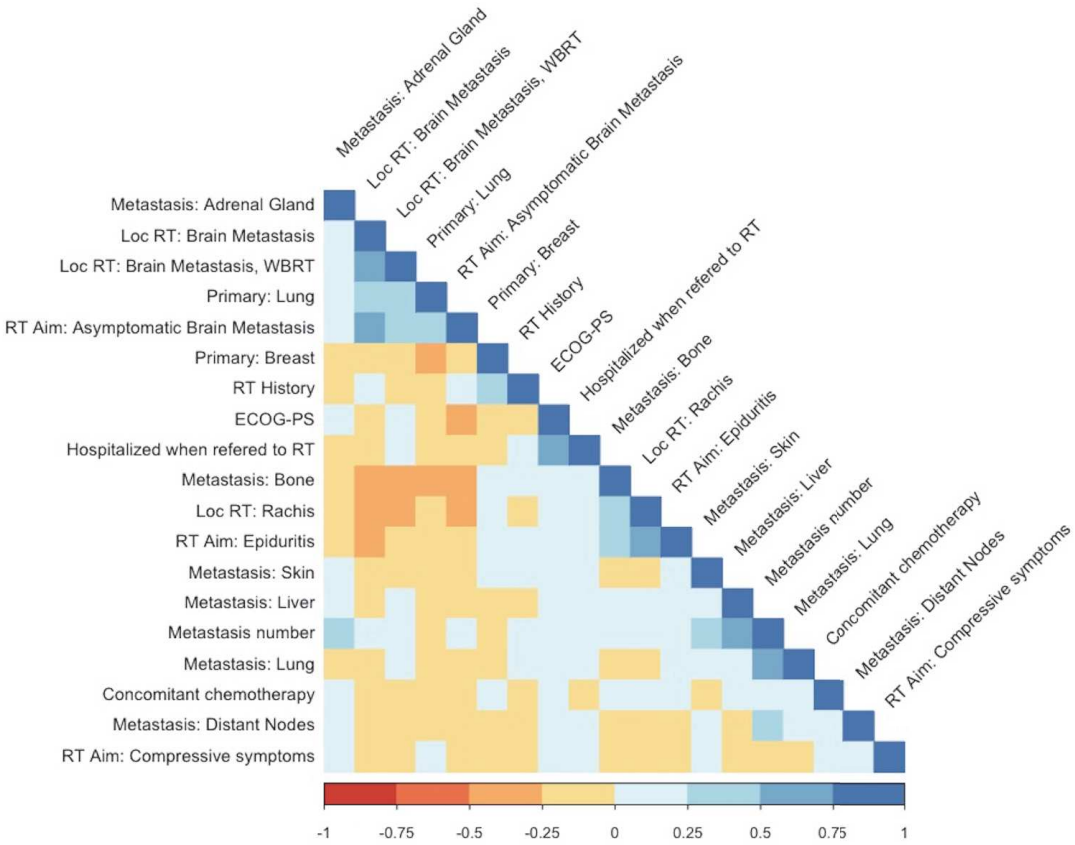


Variable 1	Variable 2	R value	R^2 value	Variable chosen for multivariate analysis
Primary: Head and Neck	Primary: Mouth	0,55	30,3%	**Primary: Head and Neck**
Metastasis number	Metastasis: Liver	0,53	27,6%	**Metastasis number**
Metastasis number	Metastasis: Lung	0,54	29,1%	**Metastasis number**
Treated site: BM, WBRT	RT's Objective: Symptomatic BM	0,51	25,7%	**RT's Objective: Symptomatic BM**
Treated site: Rachis	RT's Objective: Symptomatic epiduritis	0,63	39,6%	**RT's Objective: Symptomatic epiduritis**
ECOG-PS	Hospitalized when referred for RT	0,59	35,2%	**ECOG-PS**

Supplementary Data 2: Patients with Metastatic Disease and treated with Palliative Radiotherapy (n = 929) deceased at 7 days, 30 days and 60 days after radiotherapy: correlation test results for survival, for variables with significant p value < 0.20 in univariate analysis.
R value: correlation coefficient between variables 1 and 2 (significant I > 0.5 or < -0.5).
R^2: part of the variance in the variable 1 which can be explained by variation in the variable 2.
All correlations displayed below are significant (p < 0.001).

Deceased at 7 days

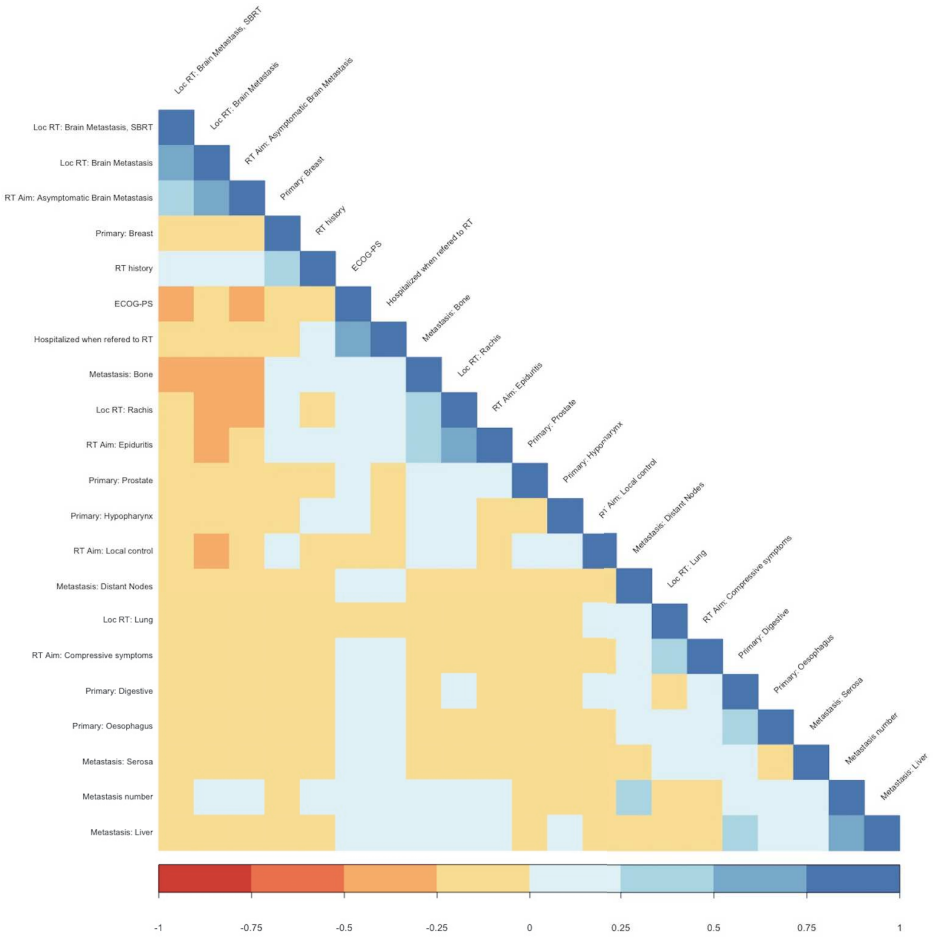
Correlation matrix



Variable 1	Variable 2	R value	R^2 value	Variable chosen for multivariate analysis
Metastasis number	Metastasis: Liver	0,53	27,6%	**Metastasis number**
Metastasis number	Metastasis: Lung	0,54	29,1%	**Metastasis number**
RT's Objective: Asymptomatic BM	Treated site: Brain	0,57	32,8%	**Treated site: Brain**
RT's Objective: Symptomatic epiduritis	Treated site: Rachis	0,63	39,6%	**RT's Objective: Symptomatic epiduritis**
ECOG-PS	Hospitalized when referred for RT	0,59	35,2%	**ECOG-PS**

Deceased at 30 days

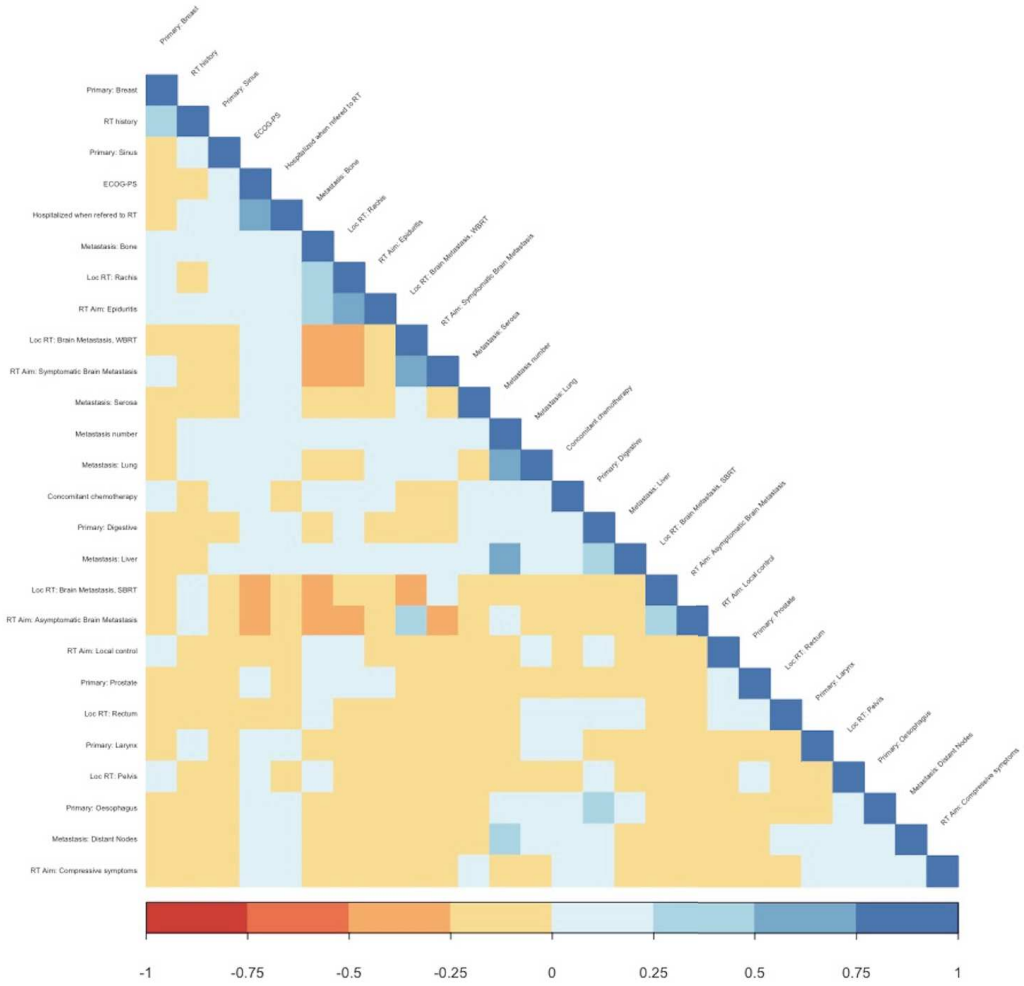
Correlation matrix



Variable 1	Variable 2	R value	R^2 value	Variable chosen for multivariate analysis
Metastasis: Liver	Metastasis number	0,53	27,6%	**Metastasis number**
RT's Objective: Asymptomatic Brain Metastasis	Treated site: Brain	0,57	32,8%	**Treated site: Brain**
Treated site: Brain Metastasis, SRT	Treated site: Brain	0,53	28,4%	**Treated site: Brain**
Treated site: Rachis	RT's Objective: Symptomatic epiduritis	0,63	39,6%	**RT's Objective: Symptomatic epiduritis**
ECOG-PS	Hospitalized when referred for RT	0,59	35,2%	**ECOG-PS**

Deceased at 60 days

Correlation matrix



Variable 1	Variable 2	R value	R^2 value	Variable chosen for multivariate analysis
Metastasis number	Metastasis: Liver	0,53	27,6%	**Metastasis number**
Metastasis number	Metastasis: Lung	0,54	29,1%	**Metastasis number**
RT's Objective: Symptomatic BM	Treated site: Brain Metastasis, WBRT	0,51	25,7%	**RT's Objective: Symptomatic BM**
RT's Objective: Symptomatic epiduritis	Treated site: Rachis	0,63	39,6%	**RT's Objective: Symptomatic epiduritis**
ECOG-PS	Hospitalized when referred for RT	0,59	35,2%	**ECOG-PS**

Abbreviations: BM: Brain metastasis – ECOG-PS: Eastern Cooperative Oncology Group- Performance Status – RT: radiotherapy – 3D-CRT: 3-dimensionnal conformational radiotherapy – IMRT: intensity-modulated radiotherapy – SRT: stereotactic radiation therapy – WBRT: whole brain radiation therapy

ARTICLE 3

"IT TAKES TWO TO KNOW ONE"
PATIENT AUTONOMY, MEDICAL DECISION MAKING AND RISK OF FUTILE RADIOTHERAPY IN PALLIATIVE CARE: CLARIFYING THE ETHICAL DEBATE THROUGH COMMUNICATION TOOLS

ABSTRACT / RÉSUMÉ

Il n'est pas aisé pour un médecin de prédire l'espérance de vie d'un patient cancéreux adressé pour soins palliatifs ; même à l'approche des derniers jours de vie, les soignants ont tendance à surestimer le pronostic des malades, une erreur de jugement qui explique déjà à elle seule une importante partie des traitements futiles. Il y a donc bien une place pour les évaluations de survie basées sur des critères objectifs, telles que les scores pronostiques.

Cependant, ces derniers ne saisissent qu'une part de la réalité clinique de la décision thérapeutique. Ils sont incapables d'intégrer les souhaits du patients, son vécu, sa lassitude, sa peur. Ils ne tiennent pas compte non plus des biais liés au médecin. En effet, d'autres études ont montré que lorsque l'on demandait à des praticiens pourquoi ils prescrivaient des traitements potentiellement futiles, au risque même de tomber dans l'obstination déraisonnable, les soignants citaient certes des raisons liées au patient (volonté exprimée de poursuivre les traitements invasifs, incompréhension et parfois déni face à la gravité du pronostic, demande des proches…) mais ils étaient également remarquablement conscients de leur propre implication, citant l'influence de leur rapport à la douleur et à la mort, de leur expérience vis-à-vis de la fin de vie, de leur difficultés à communiquer avec les malades dans ces circonstances psychologiquement et humainement très lourdes.

Afin de prévenir les traitements futiles, il semble donc essentiel de ne pas s'en tenir aux données statistiques et de s'intéresser aux mécanismes plus profonds qui sous-tendent de telles décisions, notamment au sein de la relation médecin-malade. Les principes et méthodes de raisonnement bioéthiques représentent dès lors des outils intéressants pour aborder le problème sous un autre angle et obtenir des réponses que les facteurs pronostiques cliniques ne peuvent détenir.

On peut lire la situation à travers le prisme du principlisme, théorie formulée par Beauchamp et Childress (1979) qui présente l'avantage de résumer les problématiques de bioéthiques aux conflits entre quatre principes: la bienveillance, la non-malfaisance, le principe de justice et le

respect de l'autonomie du patient. On peut donc décrire la relation médecin-malade comme une balance entre le principe de bienveillance, qui guide le devoir de soin et de compassion du praticien, et le principe d'autonomie, qui protège les valeurs du patient. Mais là encore, cette formulation du problème est incomplète: elle sous-entend notamment que le statut de personne autonome du malade est un fait inaltérable et immuable. Et quand bien même on pourrait se décider pour une définition constante de cette autonomie, le principlisme ne donne pas de solution intrinsèque pour résoudre les situations où elle entre en conflit avec le principe de bienveillance qui guide le soignant.

Ainsi, le centre de cette problématique restant la relation médecin-patient, il parait intéressant de s'intéresser à la prescription de thérapeutiques futiles à travers le prisme des modèles de communication. En effet, les différents types de relations médecin-malade décrits par Emanuel et Emanuel (1992) permettent une intéressante exploration des faiblesses du principe d'autonomie, difficile à appliquer sans nuance à un être humain malade qui souffre de ses affections physiques autant que de l'incertitude face à sa mort prochaine et dont le raisonnement est donc forcément biaisé. Le modèle de décision médicale partagée proposé par Charles et al. (1997) représente également une solution attractive pour aider le médecin à palier à la vulnérabilité de la personne souffrante sans pourtant s'ingérer dans sa décision de manière paternaliste. De plus, comme ce mode de communication est basé sur l'échange et la comparaison des valeurs individuelles, elle permet également au praticien de déceler ses propres biais et d'en tenir compte, afin d'éviter qu'ils influencent la décision thérapeutique au point qu'elle en perde son intérêt premier qui reste de servir le patient.

Une analyse approfondie de la relation médecin-patient, de leur interaction autour de la décision médicale et une formation à ces modalités de communication paraissent donc tout aussi intéressantes et nécessaires à la prévention des traitements futiles que le sont scores pronostiques et données cliniques.

"It takes two to know one"

Patient autonomy, medical decision making and risk of futile radiotherapy in palliative care: clarifying the ethical debate through communication tools

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INTRODUCTION

During the second half of the 20th century, questioning of the dominant medical paternalism led bioethicists to wonder about the patient role in medical decision making. One classical approach is to refer to the principlism initiated by Beauchamp and Childress in *Principles of Biomedical Ethics* in 1979[1]. This theory has the merit to answer biomedical issues with only four standard principles (respect of autonomy, benevolence, non-maleficence, justice), which makes it a seductively simple and adaptable tool to construct some ethical reflection upon bioethical dilemmas. One could then consider that sharing the medical decision between the physician and the patient is creating a balance between the principle of benevolence (directing the duty to care of the physician) and the autonomy principle (promoting the values of the patient).

However, acknowledging this balance is not enough to define the patient's role in the medical decision. Firstly because the principlism in itself does not imply any pre-established hierarchy between principles, nor does it propose any strong practical guideline to resolve disputes between them.* Secondly because the very definition of benevolence and autonomy may be subject to debate: if one considers only the Kantian definition of autonomy, i.e. "a property of rational will or agents"[2], then every relationship model is as valid as the next one, from the paternalist model where "patient autonomy is patient assent […] to the physician's determinations of what is best" to the informative model where "patient autonomy is patient control over medical decision making" [3].

Moreover, even if one could agree on a common definition of autonomy, it doesn't mean that it would address another particularity of the physician-patient relationship, namely that it involves caring for an ill human being and therefore acknowledging their vulnerability and

* Beauchamp and Childress did provide several ways to resolve such disputes through the years and successive editions of *Principles of Medical Bioethics* (valence of principles, intuition, reflective equilibrium, common morality…); however, the aim of this paper is to focus on a more practice-oriented method, so I will not engage a full analysis of intrinsic weaknesses of principlism.

biases. Indeed, research data tend to indicate that "many patients faced with a serious illness [and] substantial uncertainty as to the outcome […] feel extreme psychological and/or physiological vulnerability, which may make it difficult for them to participate in treatment decision-making no matter how well informed they may feel" [4]. It seems thus difficult for these patients to fully display their potential autonomy.

This indecision between the patient's will to decide for themselves and the wish to be supported is even more vivid in palliative care, when the sick person's already existing biases are amplified by the physical and psychological pain going with a symptomatic metastatic disease and an oncoming end of life.[5] Most of time, they struggle to express their fear of the unknown, they prejudge of which symptoms might be intolerable for them and they are not able to predict their own prognostic.[6]

In bioethical terms, one could then propose that this massive difficulty for the patient to act as a fully autonomous being might be balanced by the physician's benevolence. But to which point? How would a clinician decide "for the patient" which treatment is justified, which one is not? It is a well investigated fact that doctors also perform very poorly when predicting a patient's survival[7, 8], so how are they supposed to be so much more accurate on this topic than the patient himself? Are prognostic scores and clinical data enough to define what is a futile treatment and how to avoid it? Then why, in an evidence-based medical paradigm, do we still observe such an important proportion of inadequate treatments at the end of life?

A 2016 study by Willmott et al.[9] showed that there was no simple answer to that question and that futile medical care usually happened when doctors-related issues (orientation towards curative treatments, inexperience and discomfort with palliative care, poor communication skills…) met patient-related issues (poor foreseeing of the bad outcome, lack of precise information about their wishes, family's request for further curative treatments…). As the

authors pointed out, this confirmed the subjective nature of futility and the importance of communication between physicians and patients upon these difficult questions.

Therefore, in this paper, I propose to explore the physician-patient relationship, focusing around palliative care situations that may lead to futile treatment. First, I will use some bioethical principles and communication models to propose a definition of patient's autonomy. Then I will describe the model of shared decision making to suggest a modality of exchange between patient and physician capable to address the subjectivity of treatment limitation at the end life, in order to prevent the "perceived" medical futility.[9]

THE COMPLEX DEFINITION OF PATIENT AUTONOMY

First of all, when discussing a definition of patient's autonomy, one wants to acknowledge the historical context of principlism. Indeed, Beauchamp and Childress conceived their theory in the aftermath of the Belmont Report (1978), to address some important concerns raised by medical scandals occurring during the 20th century: Nazis' experiences in concentration camps during World War 2, Tuskegee's study where Afro-American patients were deliberately (and for decades) kept away from syphilis treatment by physicians employed by the U.S. government, and so on.

As David Rothman points out: "a reluctance to trust researchers to protect the well-being of their subjects soon turned into an unwillingness to trust physicians to protect the well-being of their patients"[10] and the autonomy principle was then widely interpreted not as an empowerment of the patient as an autonomous agent, but as a protection against medical domination. In the United States especially, this interpretation of autonomy became a call for patient's independency, or even "sovereignty". This sociologic particularity seems important to consider in order to explain the shift from what Emanuel and Emanuel described as a "paternalistic model" to the "informative model" [3]. (Table 1).

Relationship	Paternalistic	Informative
Patient values	Objective and shared by physician and patient	Defined, fixed, and known to the patient
Physician's obligation	Promoting the patient's well-being independently of the patient's current preferences	Providing relevant factual information and implementing patient's selected intervention
Conception of patient's autonomy	Assenting to objective values	Choice of, and control over, medical care
Conception of physician's role	Guardian	Competent technical expert

Table 1: Physician-patient relationship: paternalistic and informative relationships (from Emanuel and Emanuel,1992)

Paternalistic and informative relationships

According to Emanuel and Emanuel, the paternalistic model was promoting the physician as the patient's "guardian", considering that it was the doctor's obligation to "promot(e) the patient's well-being independent(ly) of the patient's current preferences". An interesting point in this description is the fact that the paternalist relationship is not seen as incompatible with the patient's autonomy, as the patient is still deemed a capable agent able to "[assent] to objective values". Thus in this perspective, the ethical critic one can hold against the paternalistic model is not that it doesn't respect the autonomy principle, but that it dismisses the patient's values. One can disagree with this definition, especially if one considers that patient's autonomy *is* the respect of his or her values. But it doesn't change the deeper question arising here: the ethical judgement one can express upon the paternalistic relationship depends of the very definition of the autonomy principle.

The same can be said for the opposite paradigm: the "informative model", defined by Emanuel and Emanuel as "patient choice and control over medical decisions", or in other words the total domination of patient's values upon physician's opinion. In this model, the doctor's is a technical expert "providing relevant factual information and implementing patient's selected

intervention". The autonomy principle then translates to an ability of the patient to perfectly know his or her own values and supposes that these values will stay constant in time.

This last definition seems closer of personal empowerment. However, this model implies that the patient is not only able to perfectly characterize their own values, but also that they have all abilities to understand the physician's technical explications, process them and then make a decision in full awareness of the consequences. There is no place in it for doubt, disparities in education levels, need for counselling… for any vulnerability, indeed, on the patient's side.

This view of autonomy is not only unrealistic, it can be seen as philosophically illogic. The space here doesn't allow me to discuss all the literature surrounding the definition of personhood, but I will mention the concept of "second order desires"[11], i.e. an agent's ability to form desires about his or her own desires, that according to Frankfurt characterize a person. Even if this definition can be discussed, it brings an interesting argument to this analysis: an agent is autonomous if he or she is able to not only think about his or her own values, but to evaluate them and to redefine them if needed, by putting them in balance with other values.

Then how could a patient be deemed autonomous in an informative physician-patient relationship, when their values are never confronted to the physician's ones? The very fact that the autonomy principle is defined here by patient's absolute certainty creates a paradox: if the person is constant and totally aware of his or her own values, then this person cannot engage a decision process, even less change his or her mind. Therefore, if the patient is not able to formulate desires about his or her own desires (i.e. to consider the fact these desires could change), the patient doesn't meet the definition of an autonomous being.

Moreover, even if one could agree on a common definition of autonomy, it doesn't mean that it would address another particularity of the physician-patient relationship: it involves caring for an ill human being and therefore acknowledging his or her vulnerability, especially in palliative care. Indeed, research data tend to indicate that "many patients faced with a serious

illness [and] substantial uncertainty as to the outcome […] feel extreme psychological and/or physiological vulnerability, which may make it difficult for them to participate in treatment decision-making no matter how well informed they may feel" [4]. It seems thus difficult for these patients to fully display their potential autonomy, more than ever in difficult situations such as a symptomatic metastatic disease or approaching end of life. Furthermore, patients themselves are not expecting such an "empowerment" from their relationship with their doctor: research has shown that they usually seek "information about their medical condition and treatment options without necessarily being responsible for making treatment decisions." [4, 5]

The important question is thus not if one definition of autonomy is better than another, it is which one lead to a balance which serves the patient better. The answer to that is none of the above: the paternalistic definition as well as the informative one don't allow the discussion that seems necessary for the patient to be able to make a choice, because both models exclude one protagonist from the decision making (the paternalistic excludes the patient's opinion, the informative excludes the physician's opinion) [4]. Both these attitudes may then lead to poor communication, and thereafter to futile medical care.

Interpretative and deliberative relationships

A logical solution would be then to seek another type of communication between the patient and the physician, involving both of them and their values. To answer this question, Emanuel and Emanuel suggest two other models: an interpretative one (the patient's values are predominant and the physician helps them to resolve conflict between these values by interpreting them and suggesting a solution) and a deliberative one (the doctor's values are predominant and they promotes the "most admirable" of them to the patient regarding the situation).

Both these models have their own flaws, but at least they clear the debate from any ambiguity regarding the definition of autonomy: in both cases, this principle is related to "self-understanding" and "self-development". The physician holds either the role of a "counsellor" or a "teacher". The patient's status moves from unrealistic figures of passive submission or ultimate responsibility to a more adequate role of self-aware person subject to questioning.

But self-awareness isn't enough to ensure that the patient is able to make the best decision that they could. Because even in a model where the physician recognizes patient's values and help the patient to balance them, decision in palliative care at the end of life is still going to be influenced by important bias, as it addresses the suffering of a dying human being. This person is therefore subjected to a deep vulnerability that must be acknowledged, without becoming predominant in the relationship.

ACKNOWLEDGING PATIENT'S VULNERABILITY

When discussing patient vulnerability, one wants to address how to define it, then how to manage it. I will consider vulnerability as any interference in patient's conscious decision process, either as biases directly linked to the patient or as biases tied up to the relationship with the physician. Therefore, there is a need for a communication model allowing to manage these biases, without upsetting the balance between benevolence and autonomy.

Shared decision making

One model currently considered as an "optimal approach" [12] is the "shared decision making" (SDM) process. A growing success in medical as well as patients communities [1314], especially regarding treatment of chronic and/or serious illnesses as cancer or cardiac diseases [15], it has been initially proposed by Charles et al. in 1997, and has been since described by several authors

with some variations. But the central idea behind it is to address a weakness in the interpretative and deliberative models proposed by Emanuel and Emanuel: even if they both introduce some exchange of values between patient and physician and are therefore more ethical than a pure paternalistic or informative approach, they still promote a precedence of one's values upon the other's (in the deliberative model, the physician is the one balancing benefits and harms, and in the interpretative model, the doctor only discuss patient's values without taking part in the decision itself). [16]

SDM proposes a continuum instead of an opposition, an exchange of information and values between both physician and patient, with a possible family's involvement. Furthermore, SDM insists not only on what kind of information is conveyed, but *how* it is conveyed, so that patients not only would be able to participate to the choice but that they would know that they have an active role to play in it. [16]

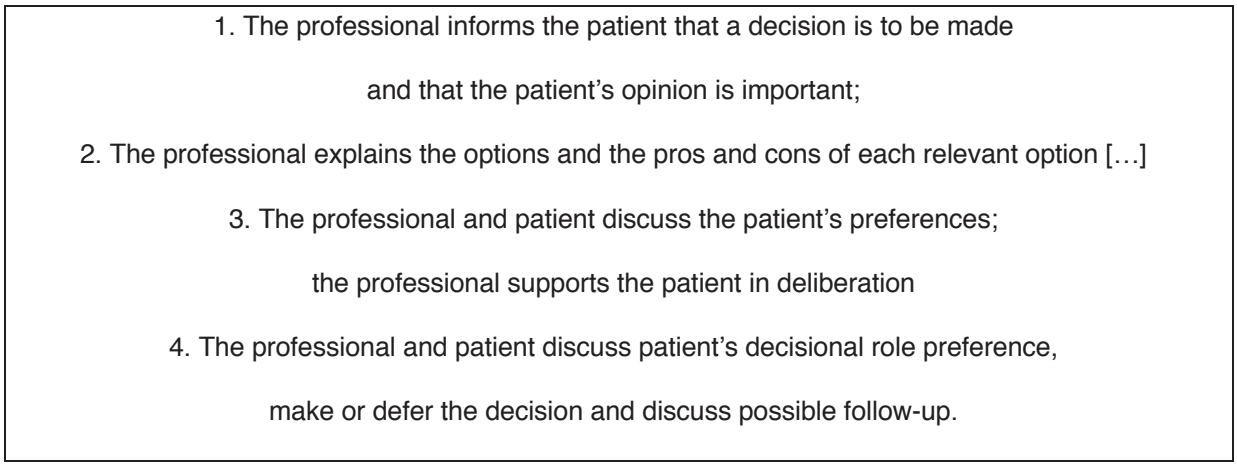
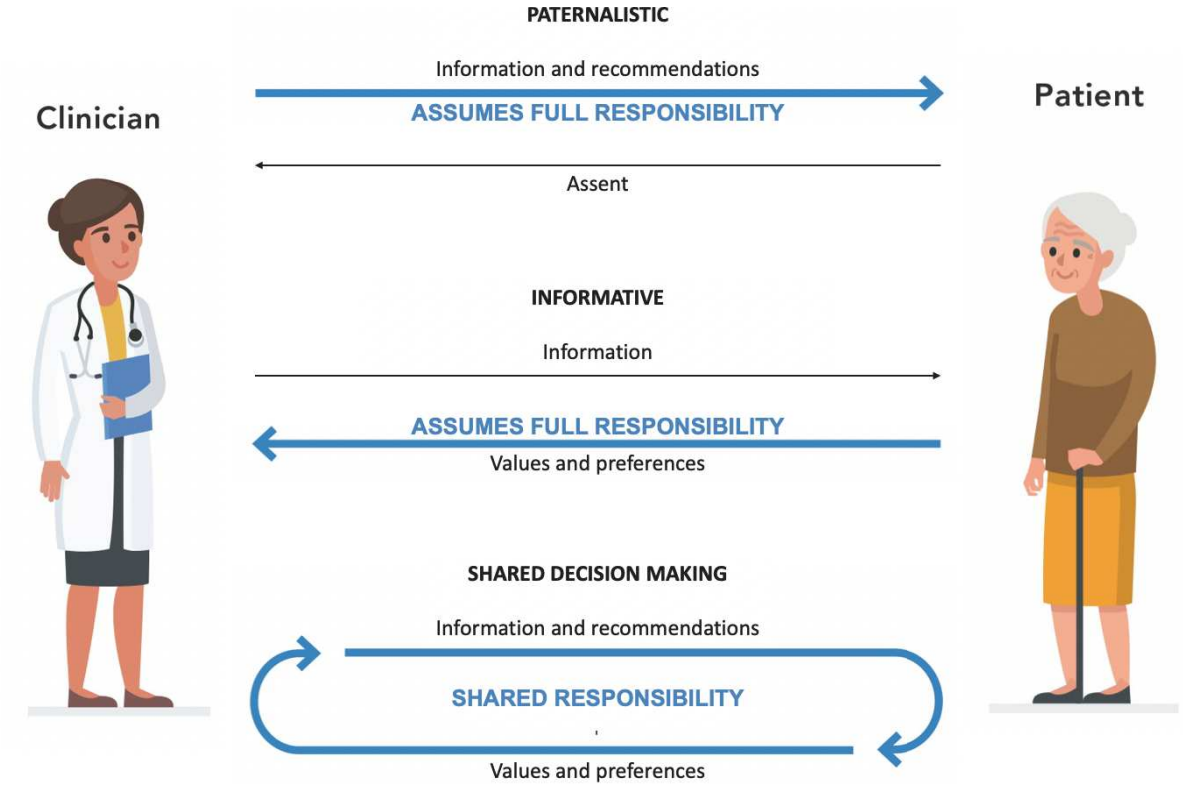


Figure 1: Example of Shared Decision Making: model with four steps (from Stiggelbout et al.)

As visible in Figure 1, if two points out of four (points 3 and 4) address the dialogue between physician and patient, the two others are directly aimed toward 1) the role that the physician wishes to give to the patient and 2) toward the role that the patient is willing to take into this decision making.

One can then conclude that the medical decision making is not only about the physician recognizing the involvement of the patient: it is about promoting it and at the same time acknowledging the fact the patient may not want to be fully involved. The patient's preference is not only in the decision itself, it also expresses in the way this decision is made. (Figure 2)



(from Charles et al., 1997) (Graphics modified from Irina Strelnikova (Shutterstock))

Patient's biases

Therefore, SDM seems a pretty elegant way of addressing many biases that can penalize the patient's decision making [6], by including the help of the physician without defining how much of their own values should be involved in the process. I will not extensively treat patient's biases, which are going from internalized family opinions and cultural influences[17] to emotional interference. But as it still is important for the physician to know about these biases to be able to recognize them and to take them in account, especially if following the SDM model, I will mention affective forecasting as a representative example.

Affective forecasting implies that patients make assumptions about their emotional adjustment to health conditions affecting their quality of life. But most of the time, they are "poor predictors of their future well-being" [18], and tend to under-estimate their abilities to cope with disability, pain and oncoming death. This fear of negative emotions can obviously influence their decision regarding a medical procedure, especially at the end of life. Halpern and Arnold specifically described three type of affective forecasting errors that might cripple the decision process: "focalism, in which people focus more on what will change than on what will stay the same; immune neglect, in which they fail to envision how their own coping skills will lessen their unhappiness; and failure to predict adaptation, in which people fail to envision shifts in what they value." [18]

This type of bias is especially relevant when analyzing communication and medical decision making, because it can be discussed and put in perspective by the physician. We then see the interest of recognizing the patient's vulnerability in the decision making process: putting the whole responsibility of such a decision upon the patient is not only ethically disputable, it can be deemed as irrelevant to the patient's best interest, as it leaves no place for addressing their difficulties and help them to decide in full awareness what really is his or her best interest.

Extrapolation to patient's family and healthcare proxy

All of above considerations regarding patient's autonomy and their implication in palliative care concern of course exclusively patients without medical impairment of their decision capacity. Nonetheless, even though the SDM was not explicitly developed to manage situations where individuals are not able to decide for themselves, it is easy to extrapolate this model to a discussion with the patient's healthcare proxy and their family. The reasoning is the same: physicians try to communicate with autonomous people in a difficult, painful situation that

makes them vulnerable and may cloud their judgement, i.e. a decision to make concerning a loved one with potential dramatical consequences.

Actually, the SDM seems particularly adapted to communication between doctors and families of an impaired patient in the specific field of palliative care. Indeed, in this situation, the emotional charge is especially heavy for the family, confronted to a loved one's oncoming death. The psychological toll for them might be very high and only increase with time, so much that they are often torn apart between their fear of losing the patient and their wish for the suffering to end. In such context, their participation to any treatment decision might be terribly guilt triggering, but their eviction of such decision may also be very destructive, as they may feel totally out of control and unable to care for their loved one. Both cases may thus lead to a demand of futile treatment, either because of personal guilt towards a decision of therapeutic limitation or because of fear to not try everything for the patient.

It seems then quite important for physicians to investigate family's values, to understand how they want to carry such a burden. SDM allows an exchange where the doctor can inform and support the patient's family, while sharing with them only the amount of responsibility that they need and want.

CONCLUSION

Respect of the individual's autonomy is essential to the physician-patient relationship, but one should stay aware that this principle in itself can be defined in many different ways, and not always in the patient best interest. The reality of medical decision is way much more complex than the sole respect of the patient’s will: especially in palliative care, patients are not perfect autonomous people in a theoretical way, they are very ill human beings, sometimes in intense physical pain and always submitted to the fear of the unknown. They don’t necessarily know

what their predominant values are, how to articulate them, how to manage their emotional biases, and the same goes for their close relatives.

That is why the physician is not a simple expert in biology manipulating prognostic factors. A doctor's role is not to take their decision depending only upon statistical findings, nor is it to disclose some dry clinical data and to let the whole responsibility of the treatment choice fall upon the sick person. Doctors are supposed, are expected to care. As our analysis of communication models showed, this implication in the final decision is not only demanded by patients [14], it is also more relevant to an ethical reading of benevolence and autonomy.

Prognostic factors will not avoid futile medical care all by themselves. Without this communication between human beings, mutually acknowledging their values, hopes and fears, no physician will be able to take a fully relevant decision and no patient will be able to decide which benefits they want and which risks they accept.

REFERENCES

1. Beauchamp T, Childress J: Principles of biomedical ethics 7ª ed. New York, Oxford University Press, 2013

2. Kant's Moral Philosophy (Stanford Encyclopedia of Philosophy) [Internet][cited 2018 Jul 13] Available from: https://plato.stanford.edu/entries/kant-moral/#Aut

3. Emanuel EJ, Emanuel LL: Four Models of the Physician-Patient Relationship. JAMA 267:2221–2226, 1992

4. Charles C, Gafni A, Whelan T: Shared decision-making in the medical encounter: What does it mean? (or it takes at least two to tango). Social Science & Medicine 44:681–692, 1997

5. Timmermans LM, van der Maazen RWM, Verhaak CM, et al: Patient participation in discussing palliative radiotherapy. Patient Education and Counseling 57:53–61, 2005

6. Edwards M, Davies M, Edwards A: What are the external influences on information exchange and shared decision-making in healthcare consultations: A meta-synthesis of the literature. Patient Education and Counseling 75:37–52, 2009

7. Glare P, Virik K, Jones M, et al: A systematic review of physicians' survival predictions in terminally ill cancer patients. BMJ 327:195, 2003

8. Kondziolka D, Parry, P. V., L. Dade Lunsford, et al: The accuracy of predicting survival in individual patients with cancer. Journal of Neurosurgery JNS 120:24–30, 2014

9. Willmott L, White B, Gallois C, et al: Reasons doctors provide futile treatment at the end of life: a qualitative study. J Med Ethics 42:496, 2016

10. Rothman D: Strangers at the bedside: a history of how law and bioethics transformed medical decision making. New York, Basic Book, 1991

11. Frankfurt H: Freedom of the will and the concept of a person. J Philosophy 68:5-20., 1971

12. Weston WW: Informed and shared decision-making: the crux of patient-centred care. CMAJ 165:438–439, 2001

13. Pollard S, Bansback N, Bryan S: Physician attitudes toward shared decision making: A systematic review. Patient Education and Counseling 98:1046–1057, 2015

14. Shay LA, Lafata JE: Understanding patient perceptions of shared decision making. Patient Education and Counseling 96:295–301, 2014

15. Joosten E a. G, DeFuentes-Merillas L, de Weert GH, et al: Systematic review of the effects of shared decision-making on patient satisfaction, treatment adherence and health status. Psychother Psychosom 77:219–226, 2008

16. Stiggelbout AM, Pieterse AH, De Haes JCJM: Shared decision making: Concepts, evidence, and practice. Patient Education and Counseling 98:1172–1179, 2015

17. Hawley ST, Morris AM: Cultural challenges to engaging patients in shared decision making. Patient Education and Counseling 100:18–24, 2017

18. Halpern J, Arnold RM: Affective Forecasting: An Unrecognized Challenge in Making Serious Health Decisions. J Gen Intern Med 23:1708–1712, 2008

« It takes two to know one » Gregory Bateson, Esalen lectures, 1975-1980

CONCLUSION DU TRAVAIL DE THESE

Au sein d'une population représentative traitée par radiothérapie, les irradiations potentiellement futiles concernaient au moins un patient sur dix, et entre un cinquième et un tiers des patients palliatifs.

Chez les malades présentant une maladie métastasique et adressés pour radiothérapie à visée symptomatique, les facteurs de risque de décès dans les deux mois suivant le traitement étaient un Performance Status inférieur à 2, des métastases dans plus de deux sites anatomiques, un cancer primitif du larynx, du pharynx ou du système digestif (rectum exclu) et une localisation tumorale médiastinale responsable de symptômes obstructifs. Les facteurs protecteurs étaient un Performance Status de 0 ou 1, l'invasion métastatique d'un unique site anatomique, un cancer primitif du sein ou de la prostate, et des métastases cérébrales asymptomatiques et accessibles à une radiothérapie en conditions stéréotaxiques.

D'autres investigations sont nécessaires afin d'accorder une valeur pronostique adéquate à chacun de ces facteurs, et une validation externe dans d'autres centres hospitaliers permettrait de confirmer les plus inattendues de ces variables, notamment la valeur péjorative d'un carcinome pharyngolaryngé ou œsophagien.

De par son effectif et sa longue période de suivi, notre base de données peut également servir à d'autres travaux, comme par exemple l'études des patients oligométastatiques ou l'identification des longs survivants, chez qui se pose le problème inverse de la radiothérapie futile: comment être efficace sur le court terme tout en évitant les effets secondaires retardés?

Enfin, il semble essentiel que les médecins impliqués dans la prise en charge des maladies graves et/ou incurables soient formés au dialogue avec le patient. Les modèles de communications tels que la décision médicale partagée ne sont pas exempts de défauts, mais ils ont le mérite de donner aux praticiens les moins expérimentés des outils pratiques pour ouvrir le dialogue, même dans des situations difficiles qui impliquent souffrance et fin de vie. Un tel échange est essentiel aussi bien pour le malade, qui voit ses valeurs respectées et ses vulnérabilités prises en compte, que pour le soignant qui peut ainsi prendre conscience de ses propres biais et éviter qu'ils parasitent sa proposition thérapeutique.

Ce n'est qu'en favorisant de telles conversations que le médecin sera en mesure d'aborder avec le patient des questions aussi délicates que celle d'un pronostic vital engagé à court terme et que le malade se sentira libre d'exprimer ses attentes vis-à-vis de cette fin de vie. En diminuant ainsi les incompréhensions mutuelles, on pourra que minimiser le risque de prise en charge inadaptée et de traitement futile.

ABREVIATIONS DE LA THESE

3D-CRT	3-Dimensional Conformational Radiation Therapy
ADK	Adenocarcinoma
BM	Brain Metastasis
CNIL	Commission Nationale de l'Informatique et des Libertés de France
DC	Ductal carcinoma
EBM	Evidence-based medicine
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
Gy	Gray
IDC	Infiltrative ductal carcinoma
ILC	Infiltrative lobular carcinoma
IMRT	Intensity Modulated Radiation Therapy
LC	Lobular carcinoma
NET	Neuroendocrine tumor
RT	Radiotherapy
SCC	Squamous cell carcinoma
SRT	Stereotactic Radiation Therapy
s.d.	Standard deviation
WBRT	Whole Brain Radiation Therapy
y.o.	Years old

CONCLUSIONS DE LA THESE

EXISTE-T-IL UNE RADIOTHERAPIE FUTILE ?

Caractéristiques cliniques des patients cancéreux décédés à moins de deux mois d'une irradiation et réflexion éthique sur le traitement par radiothérapie des malades en fin de vie

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Parmi plus de 200 000 patients atteints d'un cancer et traités par radiothérapie chaque année en France, près d'un tiers sont irradiés dans des circonstances palliatives. Pourtant la littérature s'avère assez pauvre en recommandations quant à la prise en charge de ces malades, en particulier en ce qui concerne la sélection de ceux qui sont le plus (ou moins) susceptibles de bénéficier d'une radiothérapie à visée symptomatique.

En effet, dans un contexte où l'efficacité clinique d'une irradiation est le plus souvent retardée, parfois jusqu'à huit semaines après le traitement, il peut sembler déraisonnable de proposer une radiothérapie à un malade en fin de vie. Il est cependant malaisé pour le clinicien de déterminer l'imminence du décès d'un patient en phase terminale, tout comme il est délicat de se prononcer sur l'espérance de vie d'un malade considéré comme curable mais qui présente une pathologie de mauvais pronostic ou des comorbidités majeures.

Après une revue de la littérature sur la radiothérapie futile, nous avons proposé une étude rétrospective basée sur les 3501 patients traités au service de Radiothérapie du CLCC Paul Strauss de Strasbourg entre le 1er janvier 2012 et le 1er janvier 2015. Nous avons mis en évidence les caractéristiques cliniques des malades décédés dans les deux mois qui ont suivi une irradiation, qu'ils aient été traités à visée palliative ou curative. Nous avons ensuite recherché les facteurs de risque de décès dans les deux mois chez les patients métastatiques traités par radiothérapie palliative et nous les avons articulés au sein d'un score pronostique. L'objectif était de proposer au clinicien une aide à la décision thérapeutique, dans l'idée de mieux sélectionner les malades chez qui on attend un bénéfice clinique maximal ou, au contraire, ceux pour qui l'irradiation relèvera certainement de l'inutile, voire du nuisible.

Enfin, il nous semblait essentiel de rappeler que la prise en charge d'un malade en phase terminale ne saurait s'arrêter à des paramètres purement clinico-biologiques : l'intérêt ou la futilité d'un traitement ne se résument pas à une estimation de l'espérance de vie, mais à travers une réflexion globale, centrée sur le patient et soutenue par la bienveillance, l'absence de nuisance, le respect de la justice et de l'autonomie qui sont les principes fondamentaux de la bioéthique médicale moderne. C'est pourquoi nous avons complété notre analyse par une réflexion sur la relation entre le médecin et le malade, en analysant les pistes de communication qui, associées aux facteurs pronostiques, devrait permettre de minimiser les traitements futiles et d'améliorer la prise en charge des patients cancéreux en fin de vie.

VU
Strasbourg, le 3 juillet 2019
Le Président du Jury de Thèse

Professeur Georges NOËL

VU et approuvé
Strasbourg, le 08 AOUT 2019
Le Doyen de la Faculté de Médecine de Strasbourg

Professeur Jean SIBILIA

Pour le Doyen,
L'Assesseur
Pr Bernard GOICHOT

FACULTE DE MEDECINE DE STRASBOURG
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